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71 Applicant: MERCK FROSST CANADA INC.,
16711 Trans-Canada Highway, Kirkland Quebec (CA)

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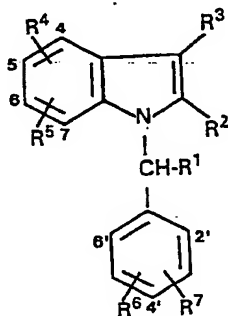
72 Inventor: Guindon, Yvan, 409 Place Closse, Ile Bizard
Quebec, H9C 1Y7 (CA)
Inventor: Gillard, John W., 710 Westchester Drive, Baie
d'Urfe Quebec, H9X 2S1 (CA)
Inventor: Yoakim, Christiane, 5770 Cote St. Luc Road,
Apt. 12, Montreal Quebec, H3X 2E5 (CA)
Inventor: Jones, Thomas R., 27 Viney Street, Kirkland
Quebec, H9J 2T2 (CA)
Inventor: Fortin, Rejean, 4820 Boul. Leger, Montreal
Quebec, H1H 1N3 (CA)

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74 Representative: Crampton, Keith John Allen et al, D
YOUNG & CO 10 Staple Inn, London WC1V 7RD (GB)

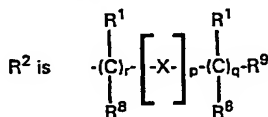
54 Indole-2-alkanoic acids and their use as prostaglandin antagonists.

57 Compounds of the formula I



where

R¹ is H or alkyl of 1 to 6 carbons or R¹ and R⁸ taken together form a group (CH₂)_v wherein v is 1 to 7;



where

each R⁸ is independently H, OH, C₁ to C₄-O-alkyl or alkyl of 1 to 4 carbons; or an R¹ and an R⁸ taken together form a group (CH₂)_v wherein v is 1 to 7,

R⁹ is COOR¹; CH₂OH; CHO; tetrazole; NHSO₂R¹⁰ wherein R¹⁰ is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN, formyl or acyl of 1 to 6 carbons; CONHSO₂R¹⁰; hydroxymethylketone; CN; or CON(R⁸)₂;

X is O; S; SO; SO₂; NR¹¹ wherein R¹¹ is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN; CR¹R⁸;

or the unit $\begin{array}{c} \text{R}^1 \\ | \\ \text{---} \text{C} = \text{C} \text{---} \\ | \\ \text{R}^8 \end{array}$ wherein the dotted line represents an optical triple bond and in which the R¹ and R⁸ substituents are absent when a triple bond is present;

r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p, q and r is 2 to 6;

R³ is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by R⁴; or C₁ to C₄ alkylphenyl or C₁ to C₄ alkylphenyl in which the phenyl is substituted by R⁴;

R⁴, R⁵, R⁶ and R⁷ are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;

(3) alkenyl having 2 to 6 carbon atoms;

(4) $-(CH_2)_nM$

wherein n is 0 to 3 and M is

a) OR^{12} ;

b) halogen;

c) CF_3 ;

d) SR^{12} ;

e) phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of R^{12} ;

f) $COOR^{13}$;



g) $C-R^{14}$;

h) tetrazole;



i) $-NH-C-R^{15}$ wherein R^{15} is C_1 to C_6 alkyl, benzyl or phenyl;

j) $-NR^{13}R^{13}$;

k) $-NHSO_2R^{16}$ wherein R^{16} is C_1 to C_6 alkyl, phenyl, or CF_3 ;



l) $-C-CH_2OH$;

m) $-SOR^{12}$;

n) $-CON^{13}R^{13}$;

o) $-SO_2NR^{13}R^{13}$;

p) $-SO_2R^{12}$;

q) NO_2 ;



r) $O-C-R^{14}$;



s) $O-C-NR^{13}R^{13}$;



t) $O-C-OR^{15}$;

u) CN ;

each R^{12} independently is H; C_1 to C_6 alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are C_1 to C_3 alkyl, halogen, CN , CF_3 , $COOR^{13}$, CH_2COOR^{13} , C_1 to C_3 alkoxy, or C_1 to C_4 perfluoroalkyl;

each R^{13} is independently H, phenyl or C_1 to C_6 alkyl; and,

each R^{14} independently is H, $(CH_2)_nCOOR^{13}$ wherein n is 0 to 4, C_1 to C_6 alkyl, CF_3 , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of R^{12} ;

and their pharmaceutically acceptable salts are useful as prostaglandin antagonists and are made into pharmaceutical compositions. Certain of the compounds are novel.

INDOLE-2-ALKANOIC ACIDS AND THEIR USE AS
PROSTAGLANDIN ANTAGONISTS

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This invention relates to prostaglandin antagonists useful in treating a variety of conditions, such as allergic asthma where excessive contractile activity of prostaglandins and prostaglandin biosynthetic intermediates occur.

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These compounds antagonize the actions of contractile prostaglandins, such as $\text{PGF}_{2\alpha}$, PGG_2 , PGH_2 , PGD_2 and TXA_2 . The use of agents which act as prostaglandin antagonists offers new approaches to therapy in a number of disease states. For example, certain prostaglandins, such as $\text{PGF}_{2\alpha}$, PGD_2 , PGG_2 , and PGH_2 , are potent contractants of bronchial muscle. Indeed human asthmatics have been shown to be especially sensitive to the bronchial constricting action of $\text{PGF}_{2\alpha}$.

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2893P/1046A

2894P/1039A

- 2 -

171021A

The compounds of the present invention also produce antithrombotic effects. Thus, they are useful in the treatment and/or prevention of thromboembolic diseases such as arterial thrombosis.

5 In addition to the involvement of contractile prostaglandins in chronic obstructive lung disease (or asthma), prostaglandins are known to play a role in other allergic conditions, as well as inflammation, diarrhea, hypertension, angina,
10 platelet aggregation, cerebral spasm, cerebral ischemia, myocardial ischemia, premature labor, spontaneous abortion, dismenorrhea, glomerular nephritis, and systemic lupus erythematosus. Consequently, the compounds of this invention will
15 alleviate the above mentioned diseases.

In addition to the prostaglandin antagonist actions, the compounds of this invention are inhibitors of the synthesis of leukotrienes. Leukotrienes B₄, C₄, D₄ and E₄ are known to
20 contribute to various disease conditions such as asthma, psoriasis, inflammation, pain, ulcers and systemic anaphylaxis. Thus inhibition of the synthesis of such compounds will alleviate these disease states.

25 The compounds of the present invention may be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; inflammatory bowel disease; ethanol-induced hemorrhagic erosions; hepatic
30 ischemia; noxious agent induced damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents

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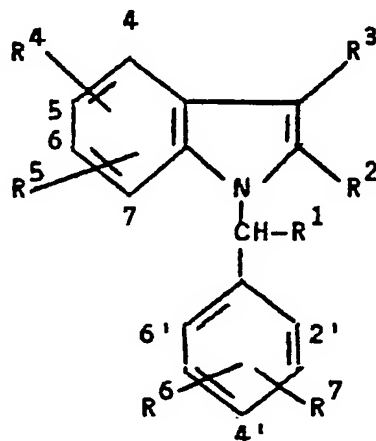
2894P/1039A

- 3 -

171021A

such as CCl_4 and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure.

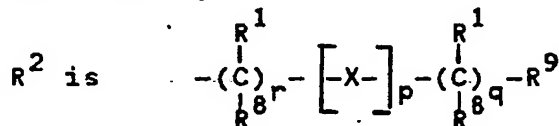
The present invention relates to a pharmaceutical composition comprising a compound of the Formula I:



I

wherein:

R^1 is H or alkyl of 1 to 6 carbons or R^1 and R^8 taken together form a group $(\text{CH}_2)_v$ wherein v is 1 to 7;



wherein:

each R^8 is independently H, OH, C_1 to C_4 -O-alkyl or alkyl of 1 to 4 carbons; or an R^1 and an R^8 taken together form a group $(\text{CH}_2)_v$ wherein v is 1 to 7.

2893P/1046A

2894P/1039A

- 4 -

171021A

R^9 is COOR^1 ; CH_2OH ; CHO ; tetrazole;
 $\text{NHSO}_2\text{R}^{10}$ wherein R^{10} is OH, alkyl or alkoxy of
 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons,
 phenyl or phenyl substituted by alkyl or alkoxy
 5 groups of 1 to 3 carbons, halogen, hydroxy, COOH , CN ,
 formyl or acyl to 1 to 6 carbons; $\text{CONHSO}_2\text{R}^{10}$;
 hydroxymethylketone; CN ; or $\text{CON}(\text{R}^8)_2$;
 X is O; S; SO ; SO_2 ; NR^{11} wherein R^{11}
 is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons,
 10 CN ; CR^1R^8 ;

or the unit $\begin{array}{c} \text{R}^1 \quad \text{R}^8 \\ | \quad | \\ -\text{C}=\text{C}- \end{array}$ wherein the dotted line
 represents an optional triple bond and in which the
 R^1 and R^8 substituents are absent when a triple
 15 bond is present;

r and q are each independently 0 to 5 and p
 is 0 or 1 provided that the total of p , q and r is 2
 to 6;

R^3 is H, alkyl of 1 to 6 carbons; phenyl
 20 or phenyl substituted by R^4 ; or C_1 to C_4 alkyl-
 phenyl or C_1 to C_4 alkylphenyl in which the
 phenyl is substituted by R^4 ;

R^4 , R^5 , R^6 and R^7 are each
 independently selected from:

- 25 (1) hydrogen;
 (2) alkyl having 1 to 6 carbon atoms;
 (3) alkenyl having 2 to 6 carbon atoms;
 (4) $-(\text{CH}_2)_n\text{M}$

wherein n is 0 to 3 and M is
 30 a) OR^{12} ;
 b) halogen;
 c) CF_3 ;

2893P/1046A

2894P/1039A

- 5 -

171021A

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- d) SR^{12} ;
 e) phenyl or substituted phenyl
 wherein substituted phenyl is
 as defined below in the
 definition of R^{12} ;

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- f) $COOR^{13}$;
 g) $\begin{array}{c} O \\ | \\ C-R^{14} \end{array}$;
 h) tetrazole;

15

- i) $-NH-\overset{\overset{O}{||}}{C}-R^{15}$ wherein R^{15} is
 C_1 to C_6 alkyl, benzyl or
 phenyl;
 j) $-NR^{13}R^{13}$;
 k) $-NHSO_2R^{16}$ wherein R^{16}
 is C_1 to C_6 alkyl,
 phenyl, or CF_3 ;

20

- l) $\begin{array}{c} O \\ || \\ -C-CH_2OH \end{array}$;
 m) $-SOR^{12}$;
 n) $-CONR^{13}R^{13}$;
 o) $-SO_2NR^{13}R^{13}$;
 p) $-SO_2R^{12}$;
 q) NO_2 ;

25

- r) $\begin{array}{c} O \\ || \\ O-C-R^{14} \end{array}$;
 s) $\begin{array}{c} O \\ || \\ O-C-NR^{13}R^{13} \end{array}$;
 t) $\begin{array}{c} O \\ || \\ O-C-OR^{15} \end{array}$;
 u) CN;

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2893P/1046A

2894P/1039A

- 6 -

171021A

each R^{12} independently is H; C_1 to C_6 alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are C_1 to C_3 alkyl, halogen, CN, CF_3 , $COOR^{13}$, CH_2COOR^{13} , C_1 to C_3 alkoxy,

5 or C_1 to C_4 perfluoroalkyl;

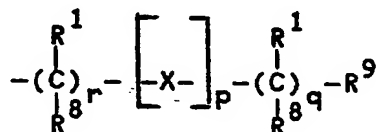
each R^{13} is independently H, phenyl or C_1 to C_6 alkyl; and,

each R^{14} independently is H, $(CH_2)_nCOOR^{13}$ wherein n is 0 to 4, C_1 to C_6 alkyl, CF_3 ,

10 phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of R^{12} ; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15 As used herein, the terms "each independently" or the equivalents thereof are employed to describe a number of possible position isomers and/or structural variations. For example, as described above, R^2 is:

20



25 The letters r and q, represent possible alkane chains of from 0 to 5 carbon atoms, each having the R^1 and R^8 substituent groups. On each carbon atom of the alkane chain, the R^1 and/or R^8 substituent may be different. The above description

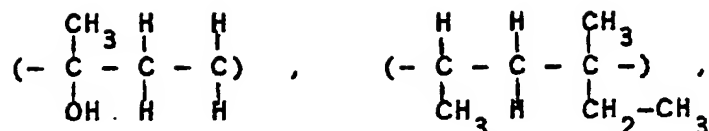
30 therefore contemplates structures such as the following for the segments $-(CR^1R^8)_r-$ and $-(CR^1R^8)_q-$:

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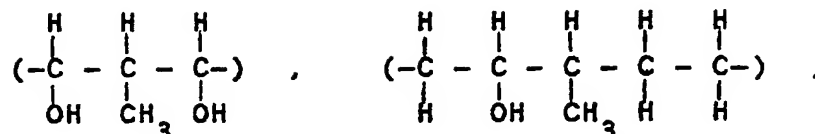
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- 7 -

171021A



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The alkyl groups referred to above may be straight chain or branched or may include cycloalkyl groups. As used herein, the term "lower" as applied to alkyl, acyl, alkoxy and the like, unless stated otherwise refers to groups having 1 to 6 carbon atoms. Halogen or halo means fluoro, chloro, bromo and/or iodo.

Pharmaceutically acceptable salts of the compounds described herein are included within the scope of the present invention. Such salts may be prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the potassium, sodium calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted

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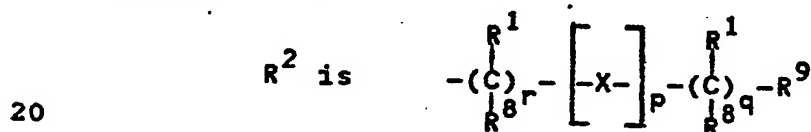
2894P/1039A

- 8 -

171021A

amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, tri-methylamine, diethanolamine, diethylamine, triethylamine, tripropylamine, 5 ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tomethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, imidazole, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines piperazine, 10 N,N-dibenzylethylenediamine, piperidine, N-ethylpiperidine, morpholine, N-ethylmorpholine, polyamine resins and the like.

Preferred compositions of the present invention comprise compounds of the Formula I wherein: 15 each R^1 is H or alkyl of 1 to 6 carbons or R^1 and R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7;



wherein:

each R^8 is independently H, OH, C_1 to C_4 -O-alkyl or alkyl of 1 to 4 carbons; or an R^1 and an R^8 taken together form a group $(CH_2)_v$ 25 wherein v is 1 to 7;

R^9 is $COOR^1$; CH_2OH ; CHO; tetrazole; $CONHSO_2R^{10}$ wherein R^{10} is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN, 30 formyl or acyl to 1 to 6 carbons; hydroxymethylketone; CN; or $CON(R^8)_2$;

2893P/1046A

2894P/1039A

- 9 -

171021A

X is O; S; SO; SO₂; NR¹¹ wherein R¹¹ is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN; CR¹R⁸;

5 or the unit $\begin{array}{c} \text{R}^1 \quad \text{R}^8 \\ | \quad | \\ -\text{C} \equiv \text{C}- \end{array}$ wherein the dotted line represents an optional triple bond and in which the R¹ and R⁸ substituents are absent when a triple bond is present;

10 r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of P, q and r is 2 to 4;

R³ is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by R⁴; or C₁ to C₄ alkyl-phenyl or C₁ to C₄ alkylphenyl in which the
15 phenyl is substituted by R⁴;

R⁴, R⁵, R⁶ and R⁷ are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- 20 (3) alkenyl having 2 to 6 carbon atoms;
- (4) $-(\text{CH}_2)_n\text{M}$ wherein n is 0 or 1 and M is
 - a) OR¹²;
 - b) halogen;
 - 25 c) CF₃;
 - d) SR¹²;
 - e) phenyl or substituted phenyl wherein substituted phenyl is as defined below in the
30 definition of R¹²;

2893P/1046A

2894P/1039A

- 10 -

171021A

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- f) COOR^{13} ;
- g) $\text{C}-\text{R}^{14}$;
- h) tetrazole;
- i) $-\text{NH}-\overset{\text{O}}{\parallel}\text{C}-\text{R}^{15}$ wherein R^{15} is C_1 to C_6 alkyl, benzyl or phenyl;
- 10 j) $-\text{NR}^{13}\text{R}^{13}$;
- k) $-\text{NHSO}_2\text{R}^{16}$ wherein R^{16} is C_1 to C_6 alkyl, phenyl, or CF_3 ;
- 15 l) $-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2\text{OH}$;
- m) $-\text{SOR}^{12}$;
- n) $-\text{CONR}^{13}\text{R}^{13}$;
- o) $-\text{SO}_2\text{NR}^{13}\text{R}^{13}$;
- 20 p) $-\text{SO}_2\text{R}^{12}$;
- q) NO_2 ;
- r) $\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{R}^{14}$;
- s) $\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{NR}^{13}\text{R}^{13}$;
- 25 t) $\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{OR}^{15}$;
- u) CN ;

each R^{12} is independently H; C_1 to C_6 alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are C_1 to C_3 alkyl, halogen, CN, CF_3 , COOR^{13} , C_1 to C_4 perfluoroalkyl; or $\text{CH}_2\text{COOR}^{13}$;

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2893P/1046A

2894P/1039A

- 11 -

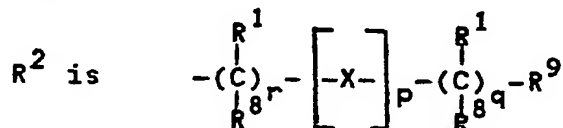
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each R^{13} is independently H, phenyl or C_1 to C_6 alkyl; and,

each R^{14} is independently H, $(CH_2)_n COOR^{13}$ wherein n is 0 to 4, C_1 to C_6 alkyl, CF_3 , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of R^{12} ; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

More preferred compositions of the present invention comprise compounds of the Formula I wherein:

R^1 is H or alkyl of 1 to 6 carbons or R^1 and R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7;



wherein:

each R^8 is independently H, OH, C_1 to C_4 -O-alkyl or alkyl of 1 to 4 carbons; or an R^1 and an R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7;

R^9 is $COOR^1$; CH_2OH ; CHO; tetrazole; hydroxymethylketone;

X is O; S; SO; SO_2 ; NR^{11} wherein R^{11} is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN; $CR^1 R^8$;

or the unit $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \equiv C- \end{array}$ wherein the dotted line represents an optional triple bond and in which the R^1 and R^8 substituents are absent when a triple bond is present;

2893P/1046A

2894P/1039A

- 12 -

171021A

r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p, q and r is 2 to 4;

5 R^3 is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by R^4 ; or C_1 to C_4 alkyl-phenyl or C_1 to C_4 alkylphenyl in which the phenyl is substituted by R^4 ;

R^4 , R^5 , R^6 and R^7 are each independently selected from:

- 10 (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- (3) alkenyl having 2 to 6 carbon atoms;
- (4) M wherein M is
 - 15 a) OR^{12} ;
 - b) halogen;
 - c) CF_3 ;
 - d) SR^{12} ;
 - 20 e) phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of R^{12} ;
 - f) $COOR^{13}$;
 - 25 g) $\begin{array}{c} O \\ || \\ C-R^{14} \end{array}$;
 - h) tetrazole;
 - i) $-NH-\begin{array}{c} O \\ || \\ C-R^{15} \end{array}$ wherein R^{15} is C_1 to C_6 alkyl, benzyl or phenyl;
 - 30 j) $-NR^{13}R^{13}$;

2893P/1046A

2894P/1039A

- 13 -

17102IA

- k) $-\text{NHSO}_2\text{R}^{16}$ wherein R^{16} is C_1 to C_6 alkyl, phenyl, or CF_3 ;

5

- l) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{CH}_2\text{OH}; \end{array}$

- m) $-\text{SOR}^{12}$ wherein R^{12} is as defined above;

10

- n) $-\text{CONR}^{13}\text{R}^{13}$;
 o) $-\text{SO}_2\text{NR}^{13}\text{R}^{13}$;
 p) $-\text{SO}_2\text{R}^{12}$;
 q) NO_2 ;

15

- r) $\begin{array}{c} \text{O} \\ \parallel \\ \text{O}-\text{C}-\text{R}^{14}; \end{array}$

- s) $\begin{array}{c} \text{O} \\ \parallel \\ \text{O}-\text{C}-\text{NR}^{13}\text{R}^{13}; \end{array}$

- t) $\begin{array}{c} \text{O} \\ \parallel \\ \text{O}-\text{C}-\text{OR}^{15}; \end{array}$

20

- u) CN ;

each R^{12} is independently H; C_1 to C_6 alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are C_1 to C_3 alkyl, halogen, CN, CF_3 , COOR^{13} , $\text{CH}_2\text{COOR}^{13}$, or C_1 to C_4 perfluoroalkyl;

25

each R^{13} is independently H, phenyl or C_1 to C_6 alkyl; and

each R^{14} is independently H, $(\text{CH}_2)_n\text{COOR}^{13}$ wherein n is 0 to 4, C_1 to C_6 alkyl, CF_3 , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of R^{12} ; or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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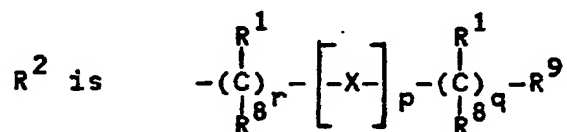
2894P/1039A

- 14 -

17102IA

Most preferred compositions of the present invention comprise compounds of the Formula I wherein:

R^1 is H or alkyl of 1 to 3 carbons or R^1 and R^8 taken together form a group $(CH_2)_{v^1}$ wherein v is 1 to 7, with the proviso that R^1 on the benzylic carbon attached to the indole nitrogen is H;



wherein:

each R^8 is independently H, or alkyl of 1 to 4 carbons; or an R^1 and an R^8 taken together form a group $(CH_2)_{v^1}$ wherein v is 1 to 7.

R^9 is $COOR^1$; CH_2OH ; CHO ; or tetrazole;

X is O; S; SO ; SO_2 ; NR^{11} wherein R^{11} is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN; CR^1R^8 ;

or the unit $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \equiv C- \end{array}$ wherein the dotted line represents an optional triple bond and in which the R^1 and R^8 substituents are absent when a triple bond is present;

r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p, q and r is 2 to 3;

R^3 is alkyl of 1 to 6 carbons, but is not cycloalkyl;

R^4 , R^5 , R^6 and R^7 are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;

2893P/1046A

2894P/1039A

- 15 -

171021A

(3) M wherein M is

- a) OR^{12} ;
- b) halogen;
- c) CF_3 ;

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- d) SR^{12} ;
- e) $-\text{SOR}^{12}$;
- f) $-\text{SO}_2\text{R}^{12}$;

10

- g) $\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^{14}$ wherein R^{14} is H,
 $(\text{CH}_2)_n\text{COOR}^{13}$ wherein n
is 0 to 4, C_1 to C_6
alkyl, CF_3 , phenyl, or
substituted phenyl wherein
substituted phenyl is as
defined above in the
definition of R^{12} ; H, C_1
to C_6 alkyl, CF_3 , phenyl
or substituted phenyl wherein
substituted phenyl is as
defined below in the
definition of R^{12} ;

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- h) CN;

each R^{12} is independently H; C_1 to C_6
25 alkyl; benzyl; phenyl or substituted phenyl wherein
the substituents are C_1 to C_3 alkyl, halogen, CN,
 CF_3 , COOR^{13} , $\text{CH}_2\text{COOR}^{13}$, wherein R^{13} is H,
phenyl, C_1 to C_6 alkyl, or C_1 to C_4
perfluoroalkyl;

30 or a pharmaceutically acceptable salt thereof, and a
pharmaceutically acceptable carrier.

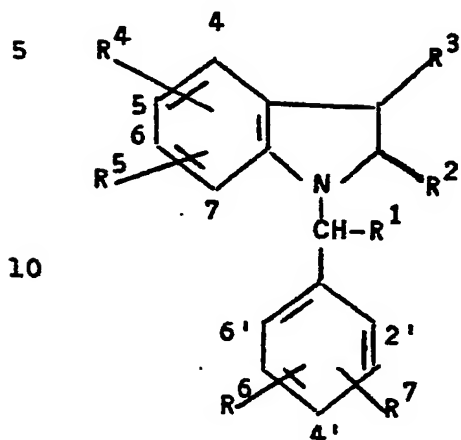
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2894P/1039A

- 16 -

171021A

The present invention also relates to novel compounds of Formula I represented by Formula Ia:



wherein:

R^1 is H or alkyl of 1 to 6 carbons or R^1 and R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7;

20 R^2 is
$$\begin{array}{c} R^1 \\ | \\ -(C)_{p'}-[-X-]_p-(C)_{p''}-R^9 \\ | \qquad \qquad | \\ R^8 \qquad \qquad R^8 \end{array}$$

wherein:

25 each R^8 is independently H, OH, C_1 to C_4 -O-alkyl, or alkyl of 1 to 4 carbons or R^1 and

R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7;

30 R^9 is $COOR^1$; CH_2OH ; CHO; tetrazole; $NHSO_2R^{10}$ wherein R^{10} is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy

2893P/1046A

2894P/1039A

- 17 -

171021A

groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN, formyl or acyl to 1 to 6 carbons; $\text{CONHSO}_2\text{R}^{10}$; hydroxymethylketone; CN; or $\text{CON}(\text{R}^8)_2$;

5 X is O; S; SO; SO_2 ; NR^{11} wherein R^{11} is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN; CR^1R^8 ;

or the unit $\begin{array}{c} \text{R}^1 \quad \text{R}^8 \\ | \quad | \\ -\text{C} \equiv \text{C}- \end{array}$ wherein the dotted line represents an optional triple bond and in which the R^1 and R^8 substituents are absent when a triple bond is present;

10 r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p, q and r is 2 to 6, with the proviso that when R^1 and R^8 are H, X is CH_2 , R^4 is 5-methoxy and R^6 is halogen, then the sums of p, q and r is 3 to 6;

15 R^3 is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by R^4 ; or C_1 to C_4 alkyl-phenyl or C_1 to C_4 alkylphenyl in which the phenyl is substituted by R^4 ;

20 R^4 , R^5 , R^6 and R^7 are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- 25 (3) alkenyl having 2 to 6 carbon atoms;
- (4) $-(\text{CH}_2)_n\text{M}$

wherein n is 0 to 3 and M is

- a) OR^{12} ;
- b) halogen;
- 30 c) CF_3 ;
- d) SR^{12} ;

2893P/1046A

2894P/1039A

- 18 -

171021A

- 5 e) phenyl or substituted phenyl
wherein substituted phenyl is
as defined below in the
definition of R^{12} ;
- f) COOR^{13} ;
- g) $\text{C}(=\text{O})\text{-R}^{14}$;
- h) tetrazole;
- 10 i) $\text{-NH-C}(=\text{O})\text{-R}^{15}$ wherein R^{15} is
 C_1 to C_6 alkyl, benzyl or
phenyl;
- j) $\text{-NR}^{13}\text{R}^{13}$;
- 15 k) $\text{-NHSO}_2\text{R}^{16}$ wherein R^{16}
is C_1 to C_6 alkyl,
phenyl, or CF_3 ;
- l) $\text{-C}(=\text{O})\text{-CH}_2\text{OH}$;
- 20 m) -SOR^{12} ;
- n) $\text{-CONR}^{13}\text{R}^{13}$;
- o) $\text{-SO}_2\text{NR}^{13}\text{R}^{13}$;
- p) $\text{-SO}_2\text{R}^{12}$;
- 25 q) NO_2 ;
- r) $\text{O-C}(=\text{O})\text{-R}^{14}$;
- s) $\text{O-C}(=\text{O})\text{-NR}^{13}\text{R}^{13}$;
- 30 t) $\text{O-C}(=\text{O})\text{-OR}^{15}$;
- u) CN ;

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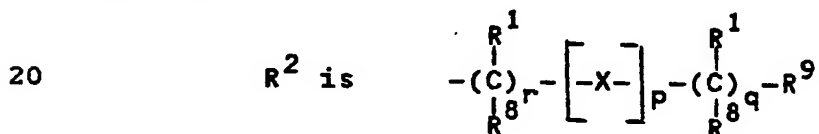
2894P/1039A

- 19 -

17102IA

- each R^{12} is independently H; C_1 to C_6 alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are C_1 to C_3 alkyl, halogen, CN, CF_3 , $COOR^{13}$, CH_2COOR^{13} C_1 to C_3 alkoxy, or
- 5 C_1 to C_4 perfluoroalkyl;
- each R^{13} is independently H, phenyl or C_1 to C_6 alkyl;
- each R^{14} is independently H, $(CH_2)_nCOOR^{13}$ wherein n is 0 to 4, C_1 to C_6 alkyl, CF_3 ,
- 10 phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of R^{12} ; or a pharmaceutically acceptable salt thereof.

- Preferred novel compounds of the present
- 15 invention are compounds of the Formula Ia wherein:
- R^1 is H or alkyl of 1 to 6 carbons or R^1 and R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7;



wherein:

- each R^8 is independently H, OH, C_1 to C_4 -O-alkyl, or alkyl of 1 to 4 carbons or R^1 and
- 25 R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7;
- R^9 is $COOR^1$; CH_2OH ; CHO; tetrazole; $CONHSO_2R^{10}$ wherein R^{10} is OH, alkyl or alkoxy
- 30 of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN,

2893P/1046A

2894P/1039A

- 20 -

171021A

formyl or acyl to 1 to 6 carbons; hydroxymethyl-
ketone; CN; or $\text{CON}(\text{R}^8)_2$;

X is O; S; SO; SO_2 ; NR^{11} wherein R^{11}
is H, alkyl of 1 to 6 carbons, acyl of 1 to 6
5 carbons, CN; $\text{CR}^{\text{L}8}$;
 $\text{R}^{\text{L}1} \text{R}^8$

or the unit $-\text{C} \equiv \text{C}-$ wherein the dotted line
represents an optional triple bond and in which the
 $\text{R}^{\text{L}1}$ and R^8 substituents are absent when a triple
10 bond is present;

r and q are each independently 0 to 5 and p
is 0 or 1 provided that the total of p, q and r is 2
to 4, with the proviso that when $\text{R}^{\text{L}1}$ and R^8 are H,
X is CH_2 , R^4 is 5-methoxy and R^6 is halogen,
15 then the sums of p, q and r is 3 to 4;

R^3 is H, alkyl of 1 to 6 carbons; phenyl
or phenyl substituted by R^4 ; or C_1 to C_4 alkyl-
phenyl or C_1 to C_4 alkylphenyl in which the
phenyl is substituted by R^4 ;

20 R^4 , R^5 , R^6 and R^7 are each
independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- (3) alkenyl having 2 to 6 carbon atoms;
- 25 (4) $-(\text{CH}_2)_n \text{M}$

wherein n is 0 or 1 and M is

- a) OR^{12} ;
- b) halogen;
- c) CF_3 ;
- 30 d) SR^{12} ;

2893P/1046A

2894P/1039A

- 21 -

171021A

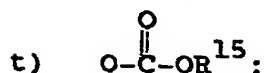
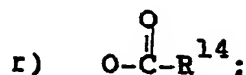
- 5 e) phenyl or substituted phenyl
wherein substituted phenyl is
as defined below in the
definition of R^{12} ;
- f) $COOR^{13}$;
- 10 g) $\overset{O}{\parallel}C-R^{14}$ wherein R^{14} is H,
 $(CH_2)_nCOOR^{13}$ wherein n
is 0 to 4, C_1 to C_6
alkyl, CF_3 , phenyl, or
substituted phenyl wherein
substituted phenyl is as
defined below in the
definition of R^{12} ;
- 15 h) tetrazole;
- i) $-\overset{O}{\parallel}NH-C-R^{15}$ wherein R^{15} is
 C_1 to C_6 alkyl, benzyl or
phenyl;
- 20 j) $-NR^{13}R^{13}$;
- k) $-NHSO_2R^{16}$ wherein R^{16}
is C_1 to C_6 alkyl,
phenyl, or CF_3 ;
- 25 l) $\overset{O}{\parallel}C-CH_2OH$;
- m) $-SOR^{12}$;
- n) $-CONR^{13}R^{13}$;
- o) $-SO_2NR^{13}R^{13}$;
- 30 p) $-SO_2R^{12}$;
- q) NO_2 ;

2893P/1046A

2894P/1039A

- 22 -

171021A



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each R^{12} is independently H; C_1 to C_6 alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are C_1 to C_3 alkyl, halogen, CN, CF_3 , COOR^{13} , $\text{CH}_2\text{COOR}^{13}$, C_1 to C_3 alkoxy C_1 to C_4 perfluoroalkyl;

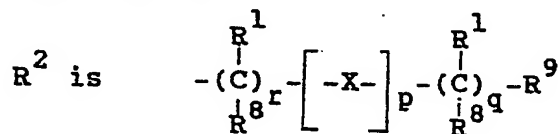
each R^{13} is independently H, phenyl or C_1 to C_6 alkyl;

each R^{14} is independently H, $(\text{CH}_2)_n\text{COOR}^{13}$ wherein n is 0 to 4, C_1 to C_6 alkyl, CF_3 , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of R^{12} ;

or a pharmaceutically acceptable salt thereof.

More preferred novel compounds of the present invention are compounds of the formula Ia wherein:

R^1 is H or alkyl of 1 to 6 carbons or R^1 and R^8 taken together form a group $(\text{CH}_2)_v$ wherein v is 1 to 7;



wherein:

each R^8 is independently H, OH, C_1 to C_4 -O-alkyl, or alkyl of 1 to 4 carbons or R^1 and

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2893P/1046A

2894P/1039A

- 23 -

171021A

R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7;

R^9 is $COOR^1$; CH_2OH ; CHO ; tetrazole; hydroxymethylketone;

5 X is O ; S ; SO ; SO_2 ; NR^{11} wherein R^{11} is H , alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN ; CR^1R^8 ;

10 or the unit $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \cdots C- \end{array}$ wherein the dotted line represents an optional triple bond and in which the R^1 and R^8 substituents are absent when a triple bond is present;

15 r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p , q and r is 2 to 4, with the proviso that when R^1 and R^8 are H , X is CH_2 , R^4 is 5-methoxy and R^6 is halogen, then the sums of p , q and r is 3 to 4;

20 R^3 is H , alkyl of 1 to 6 carbons; phenyl or phenyl substituted by R^4 ; or C_1 to C_4 alkyl-phenyl or C_1 to C_4 alkylphenyl in which the phenyl is substituted by R^4 ;

R^4 , R^5 , R^6 and R^7 are each independently selected from:

- (1) hydrogen;
- 25 (2) alkyl having 1 to 6 carbon atoms;
- (3) alkenyl having 2 to 6 carbon atoms;
- (4) M wherein M is
 - a) OR^{12} ;
 - b) halogen;
 - 30 c) CF_3 ;

2893P/1046A

2894P/1039A

- 24 -

171021A

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- d) SR^{12} ;
 e) phenyl or substituted phenyl
 wherein substituted phenyl is
 as defined below in the
 definition of R^{12} ;

10

- f) COOR^{13} ;
 O
 \parallel
 g) C-R^{14} ;
 h) tetrazole;

15

- i) $-\text{NH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^{15}$ wherein R^{15} is
 C_1 to C_6 alkyl, benzyl or
 phenyl;
 j) $-\text{NR}^{13}\text{R}^{13}$;
 k) $-\text{NHSO}_2\text{R}^{16}$ wherein R^{16}
 is C_1 to C_6 alkyl,
 phenyl, or CF_3 ;

20

- O
 \parallel
 l) $-\text{C}-\text{CH}_2\text{OH}$;

25

- m) $-\text{SOR}^{12}$;
 n) $-\text{CONR}^{13}\text{R}^{13}$;
 o) $-\text{SO}_2\text{NR}^{13}\text{R}^{13}$;
 p) $-\text{SO}_2\text{R}^{12}$;
 q) NO_2 ;

30

- O
 \parallel
 r) $\text{O}-\text{C}-\text{R}^{14}$;
 O
 \parallel
 s) $\text{O}-\text{C}-\text{NR}^{13}\text{R}^{13}$;
 O
 \parallel
 t) $\text{O}-\text{C}-\text{OR}^{15}$;
 u) CN ;

2893P/1046A

2894P/1039A

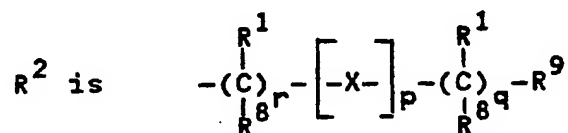
- 25 -

171021A

- each R^{12} is independently H; C_1 to C_6 alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are C_1 to C_3 alkyl, halogen, CN, CF_3 , $COOR^{13}$, CH_2COOR^{13} , C_1 to C_3 alkoxy or
- 5 C_1 to C_4 perfluoroalkyl;
- each R^{13} is independently H, phenyl or C_1 to C_6 alkyl; and
- each R^{14} is H, $(CH_2)_nCOOR^{13}$ wherein n is 0 to 4, C_1 to C_6 alkyl, CF_3 , phenyl, or
- 10 substituted phenyl wherein substituted phenyl is as defined above in the definition of R^{12} ;
- or a pharmaceutically acceptable salt thereof.

- Most preferred novel compounds of the
- 15 present invention are compounds of the formula Ia wherein:

- R^1 is H or alkyl of 1 to 3 carbons or R^1 and R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7, with the proviso that R^1 on
- 20 the benzylic carbon attached to the indole nitrogen is H;



- 25 wherein:

- each R^8 is independently H, OH, C_1 to C_4 -O-alkyl or alkyl of 1 to 4 carbons or R^1 and
- R^8 taken together form a group $(CH_2)_v$ wherein v
- 30 is 1 to 7;
- R^9 is $COOR^1$; CH_2OH ; CHO; or tetrazole;

0166591

2893P/1046A

2894P/1039A

- 26 -

171021A

X is O; S; SO; SO₂; NR¹¹ wherein R¹¹ is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN; CR¹R⁸;

5 or the unit $\begin{array}{c} \text{R}^1 \quad \text{R}^8 \\ | \quad | \\ -\text{C} \equiv \text{C}- \end{array}$ wherein the dotted line represents an optional triple bond and in which the R¹ and R⁸ substituents are absent when a triple bond is present;

10 r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p, q and r is 2 to 3, with the proviso that when R¹ and R⁸ are H, X is CH₂, R⁴ is 5-methoxy and R⁶ is halogen, then the sum of r, p and q is 3 to 4;

15 R³ is alkyl of 1 to 6 carbons, but not cycloalkyl;

R⁴, R⁵, R⁶ and R⁷ are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- 20 (3) M wherein M is
 - a) OR¹²;
 - b) halogen;
 - c) CF₃;
 - 25 d) SR¹²;
 - e) -SOR¹²;
 - f) -SO₂R¹²;
 - 30 g) $\begin{array}{c} \text{O} \\ || \\ \text{O}-\text{C}-\text{R}^{14} \end{array}$, wherein R¹⁴ is H, C₁ to C₆ alkyl, CF₃, phenyl or substituted phenyl wherein substituted phenyl is

2893P/1046A

2894P/1039A

- 27 -

171021A

as defined below in the
definition of R^{12} ;

h) CN;

- each R^{12} is independently H; C_1 to C_6
alkyl; benzyl; phenyl or substituted phenyl wherein
the substituents are C_1 to C_3 alkyl, halogen, CN,
 CF_3 , $COOR^{13}$, CH_2COOR^{13} , C_1 to C_3 alkoxy;
or C_1 to C_4 perfluoroalkyl;
each R^{13} is independently H, phenyl or
 C_1 to C_6 alkyl;
or a pharmaceutically acceptable salt thereof.

Most-particularly preferred novel compounds
of the present invention are compounds of the formula
Ia wherein:

R^1 is H or alkyl of 1 to 3 carbons, with
the proviso that R^1 on the benzylic carbon attached
to the indole nitrogen is H;

R^2 is
$$\begin{array}{c} R^1 \\ | \\ -(C)_{r-} \\ | \\ R^8 \end{array} [-X-]_p \begin{array}{c} R^1 \\ | \\ -(C)_{q-} \\ | \\ R^8 \end{array} -R^9$$

wherein:

each R^8 is independently H or alkyl of 1
to 4 carbons, with the proviso that at least one of
the R^1 or R^8 substituents in R^2 is not hydrogen;

R^9 is $COOH$; CH_2OH ; CHO ; or tetrazole;

X is CR^1R^8 ;

r and q are each independently 0 to 3 and p
is 0 or 1 provided that the total of p , q and r is 2
to 3;

R^3 is alkyl of 1 to 6 carbons, but not
cycloalkyl;

2893P/1046A

2894P/1039A

- 28 -

171021A

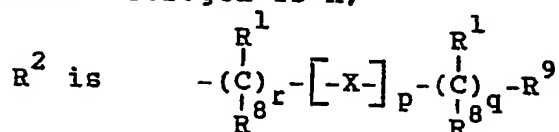
R^4 , R^5 , R^6 and R^7 are each
independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- 5 (3) M wherein M is
 - a) OR^{12} ;
 - b) halogen;
 - c) CF_3 ;
 - 10 d) SR^{12} ;
 - e) $-SOR^{12}$;
 - f) $-SO_2R^{12}$;
 - 15 g) $O-\overset{\overset{O}{\parallel}}{C}-R^{14}$, wherein R^{14} is H,
 C_1 to C_6 alkyl, CF_3 ,
 phenyl or substituted phenyl
 wherein substituted phenyl is
 as defined below in the
 definition of R^{12} ;
 - 20 h) CN;

each R^{12} is independently H; C_1 to C_6
alkyl; or benzyl;
or a pharmaceutically acceptable salt thereof.

25 Other most-particularly preferred novel
compounds of the present invention are compounds of
the formula Ia wherein:

R^1 is H or alkyl of 1 to 3 carbons, with
the proviso that R^1 on the benzylic carbon attached
30 to the indole nitrogen is H;



2893P/1046A

2894P/1039A

- 29 -

17102IA

wherein:

each R^8 is independently H or alkyl of 1 to 4 carbons;

R^9 is COOH; CH_2OH ; CHO; or tetrazole;

5 X is O; S; SO; or SO_2 ;

r and q are each independently 0 to 3 and p is 1 provided that the total of p, q and r is 2 to 3;

R^3 is alkyl of 1 to 6 carbons, but not cycloalkyl;

10 R^4 , R^5 , R^6 and R^7 are each independently selected from:

(1) hydrogen;

(2) alkyl having 1 to 6 carbon atoms;

(3) M wherein M is

15 a) OR^{12} ;

b) halogen;

c) CF_3 ;

d) SR^{12} ;

20 e) $-SOR^{12}$;

f) $-SO_2R^{12}$;

g) $O-\overset{\overset{O}{\parallel}}{C}-R^{14}$, wherein R^{14} is H, C_1 to C_6 alkyl, CF_3 , phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of R^{12} ;

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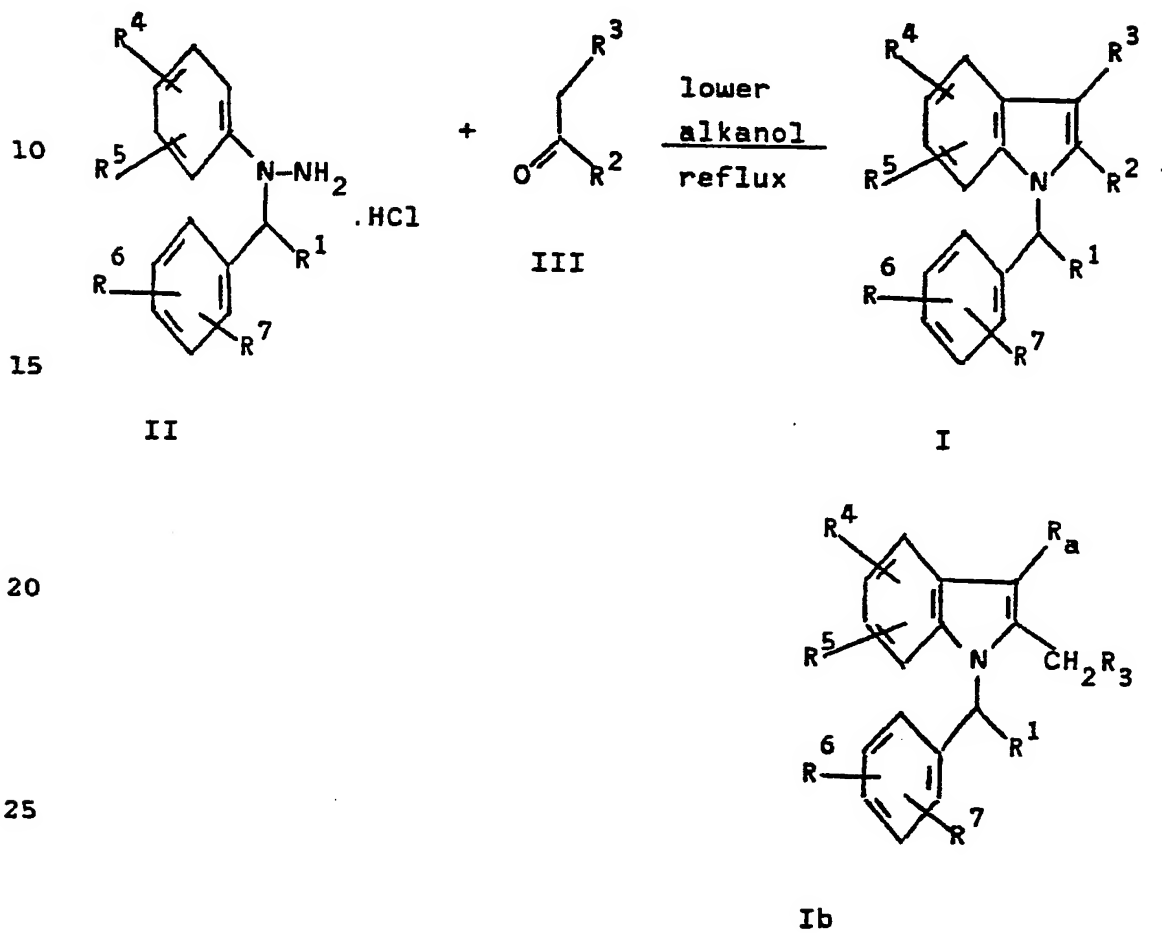
h) CN;

30 each R^{12} is independently H; C_1 to C_6 alkyl; or benzyl;

or a pharmaceutically acceptable salt thereof.

The following reaction schemes illustrate the preparation of the compounds of the present invention:

5 Scheme I Preparation of Formula I Compounds

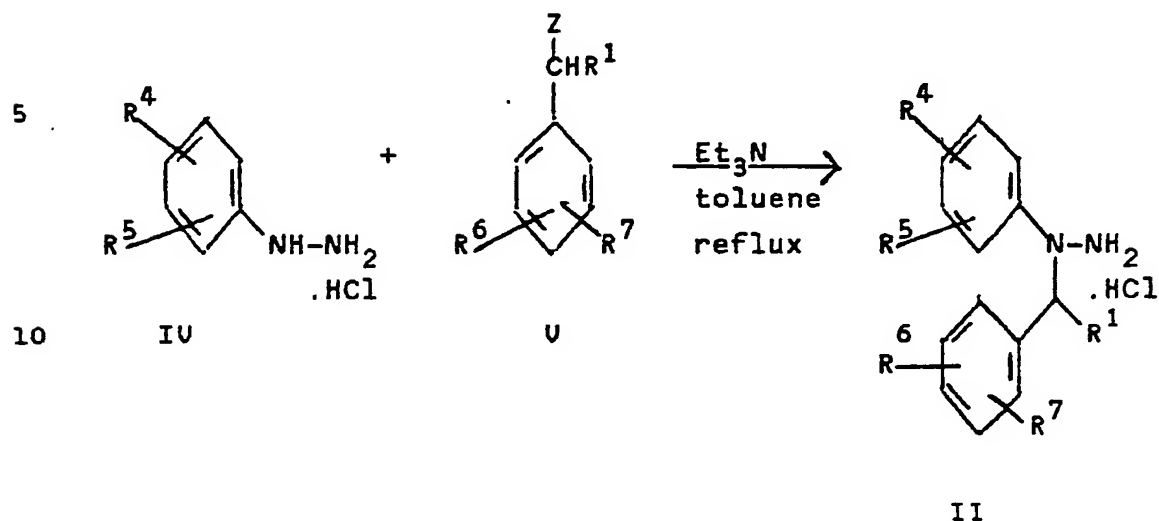


2893P/1046A

2894P/1039A

- 31 -

17102IA

Scheme II Preparation of Hydrazine Derivatives (II)

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With regard to Scheme I, the alkanol solvent can have an important effect on the course of the reaction. With some of the ketones III, the final product may contain a mixture of the isomers I and Ib. Formation of the undesired Ib is minimized by using isopropanol or tert-butanol in place of methanol or ethanol.

The sequence described above is an application of the Fischer Indole Synthesis.

25 Numerous indole syntheses are described in reviews, such as, for example "Heterocyclic Compounds" Volume 25, Parts I, II, III, W. J. Houlihan (Ed.), Interscience, J. Wiley & Sons, N. Y., 1979.

Appropriate manipulations of functional groups using sequences described in such reviews will lead to the compounds of the present invention. Another useful

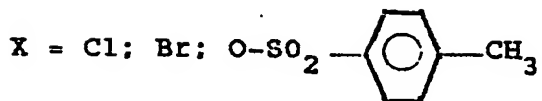
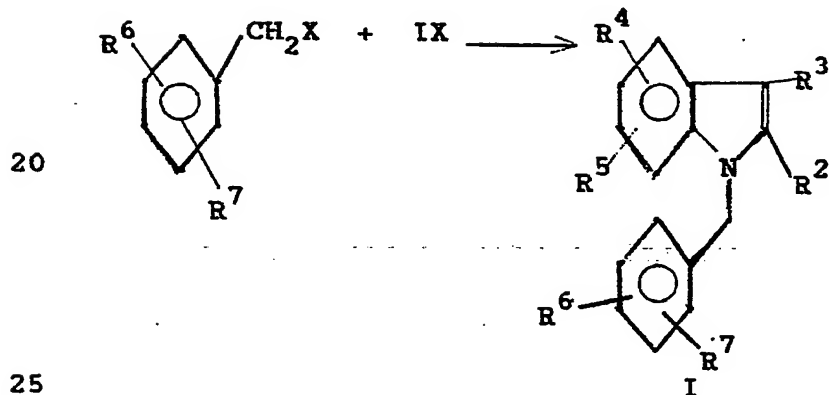
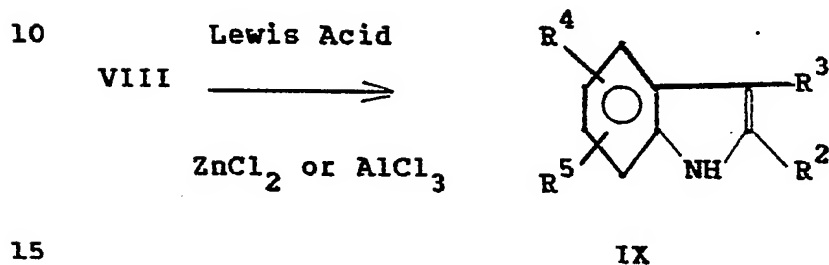
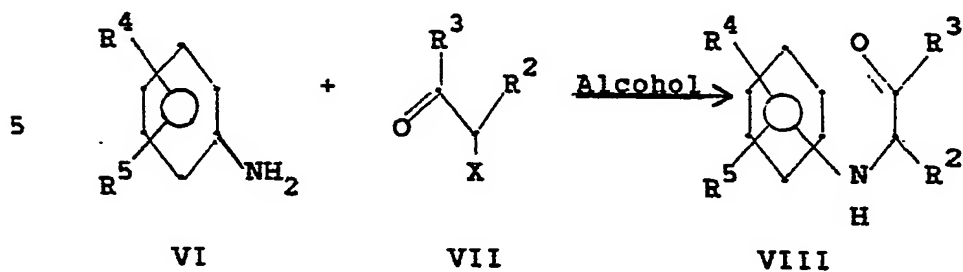
30 sequence is shown in Scheme III.

2893P/1046A

2894P/1039A

- 32 -

171021A

Scheme III Preparation of Indole-2-Alkanoic acids

30 The Bischler Indole Synthesis used in the sequence described for the synthesis of compounds of the present invention envisages the alkylation of an

0166591

2893P/1046A

2894P/1039A

- 33 -

171021A

appropriately substituted halo or tosyloxy ketone
(VII) by an appropriately substituted aniline
derivative (VI), in an alcoholic solvent. The
condensation step is effected through the use of a
5 Lewis Acid or mineral acid. The indole derivative so
produced (IX) may then be alkylated by an
aralkylhalide to product I.

The following ketones (1-7) of structure III
10 are known in the art:

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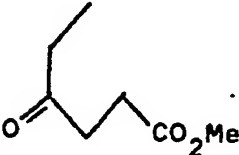
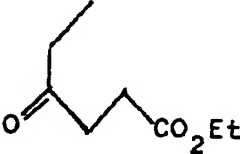
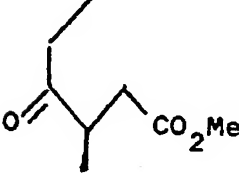
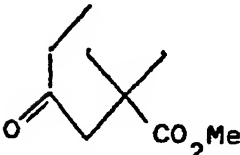
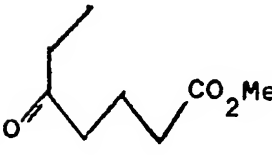
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2894P/1039A

- 34 -

17102IA

TABLE 1Ketones of Formula III

5	<u>No.</u>	<u>Structure</u>	<u>Reference</u>
10	1.		Methyl 4-oxohexanoate: B. L. Feringa and W. Dannenberg, Synth. Commun., <u>13</u> , 509-514 (1983).
15	2.		Ethyl 4-oxohexanoate: D. A. Wehrli and V. Chu, Org. Synth., <u>58</u> , 79-82 (1978).
20	3.		3-Methyl-4-oxohexanoate: A. P. Cowling and J. Mann, J. Chem. Soc., Chem. Commun., 1006-1007 (1978).
25	4.		Methyl 2,2-dimethyl-4-oxohexanoate: R. Scarpati, G. Scherillo, F. Imperato and R. A. Nicolaus, Gazz. Chim. Ital., <u>97</u> , 654-664 (1967).
30	5.		Methyl 5-oxoheptanoate: M. K. Eberle and G. G. Kahle, Tetrahedron Lett., <u>21</u> , 2303-2304 (1980).

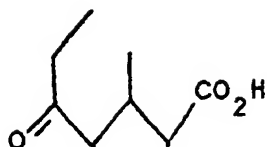
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- 35 -

171021A

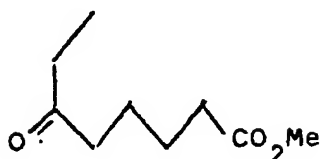
6.



3-Methyl-5-oxoheptanoic
acid: C. Conti,

A. Niccoli and R. Rossi,
Chim. Ind. (Milan) 58: 877
(1976).

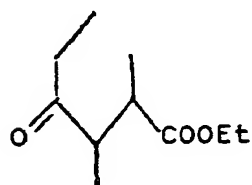
7.



Methyl 6-oxooctanoate:

T. Terasawa and T. Okada,
Tetrahedron 33, 595-598
(1977).

8.



Ethyl 2,3-dimethyl-4-oxo-
hexanoate

Examples of Formula I compounds useful in
the pharmaceutical compositions of the present
invention are tabulated below. The numbers preceding
the R⁴, R⁵, R⁶, and R⁷ definitions indicate
the substituent position in the structure. Standard
abbreviations such as Me for methyl, Et for ethyl, Pr
for propyl, Bu for butyl, Ac for acetyl, and Ph for
phenyl are used. Compounds 3 to 72 are novel
compounds.

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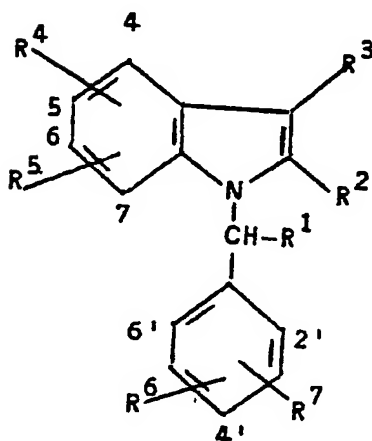
2893P/1046A

2894P/1039A

- 36 -

17102IA

TABLE 2

Compounds of the Formula I

I

Compound		R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷
No.								
20	1	H	(CH ₂) ₂ CO ₂ H	Me	5-OMe	H	4'-Cl	H
	2	H	(CH ₂) ₂ CO ₂ Me	Me	5-OMe	H	4'-Cl	H
	3	H	(CH ₂) ₂ CO ₂ H	Me	5-F	H	4'-Cl	H
	4	H	(CH ₂) ₂ CO ₂ H	Me	4-Cl	6-Cl	4'-Cl	H
	5	H	(CH ₂) ₂ CO ₂ H	Me	4-OMe	H	4'-Cl	H
25	6	H	(CH ₂) ₂ CO ₂ H	Me	6-OMe	H	4'-Cl	H
	7	H	(CH ₂) ₂ CO ₂ H	Me	4-Me	H	4'-Cl	H
	8	H	(CH ₂) ₂ CO ₂ H	Me	6-Me	H	4'-Cl	H
	9	H	(CH ₂) ₄ CO ₂ H	Me	5-OMe	H	4'-Cl	H
	10	H	(CH ₂) ₂ CO ₂ H	Me	5-Me	H	4'-Cl	H
30	11	H	(CH ₂) ₃ CO ₂ H	Me	5-OMe	H	4'-Cl	H
	12	H	(CH ₂) ₂ CO ₂ H	Me	5-OH	H	4'-Cl	H
	13	H	(CH ₂) ₂ CO ₂ H	Me	5-Cl	H	4'-Cl	H

0166591

2893P/1046A

2894P/1039A

- 37 -

171021A

Compound								
No.		R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷
14	H	(CH ₂) ₂	CO ₂ H	Me	H	H	4'-Cl	H
15	H	(CH ₂) ₂	CO ₂ H	Me	5-Br	H	4'-Cl	H
5							O	
16	H	(CH ₂) ₂	CO ₂ H	Me	5-OMe	H	4'-S-Me	H
17	H	(CH ₂) ₂	CO ₂ H	Me	5-OMe	H	4'-SMe	H
18	H	(CH ₂) ₃	CO ₂ H	Me	5-OMe	H	4'-SMe	H
19	H	(CH ₂) ₃	CO ₂ H	Me	5-F	H	4'-Cl	H
10	20	H	(CH ₂) ₂	CO ₂ H	Me	5-F	4'SMe	H
							O	
21	H	(CH ₂) ₂	CO ₂ H	Me	5-F	H	4'-S-Me	H
22	H	CH(Me)CH ₂	CO ₂ H	Me	5-OMe	H	4'-Cl	H
23	H	CH ₂ OCH ₂	CO ₂ H	Me	5-OMe	H	4'-Cl	H
15	24	H	(CH ₂) ₂	CO ₂ H	Me	5-OAc	4'-Cl	H
25	H	CH ₂ CH(Me)CH ₂	CO ₂ H	Me	5-OMe	H	4'-Cl	H
26	H	(CH ₂)CH(Me)CH ₂	CO ₂ H	H	5-F	H	4'-Cl	H
27	H	CH ₂ C(Me) ₂	CO ₂ H	H	5-OMe	H	4'-Cl	H
28	H	(CH ₂) ₃	CO ₂ H	Me	5-F	H	4'-SMe	H
20	29	H	(CH ₂) ₂	CO ₂ H	Me	5-OMe	H	H
30	H	(CH ₂) ₂	CO ₂ H	Me	H	H	H	H
31	H	(CH ₂) ₂	CO ₂ H	Me	5-OMe	H	4'-CF ₃	H
32	H	(CH ₂) ₂	CO ₂ H	Me	5-OMe	H	4-SMe	H
33	H	(CH ₂) ₂	CO ₂ H	Me	5-OMe	H	4-SMe	H
25							O	
34	H	(CH ₂) ₂	CO ₂ H	Me	5-OMe	H	4'-SMe	H
							O O	
35	H	(CH ₂) ₂	CO ₂ H	Me	5-F	H	4'-Cl	H
36	H	(CH ₂) ₂	CO ₂ H	Me	5-Cl	H	4'-Cl	H
30	37	H	(CH ₂) ₂	CO ₂ H	Me	5-Br	4'-Cl	H
38	Me	(CH ₂) ₂	CO ₂ H	Me	5-OMe	H	4'-Cl	H
39	H	(CH ₂) ₂	CO ₂ H	Et	5-OMe	H	4'-Cl	H

0166591

2893P/1046A

2894P/1039A

- 38 -

171021A

	40	H	$(\text{CH}_2)_2\text{CO}_2\text{H}$	Me	5-OH	H	4'-Cl	H
	41	H	$(\text{CH}_2)_2\text{CO}_2\text{H}$	Me	5-OAc	H	4'-Cl	H
	42	H	$(\text{CH}_2)_2\text{CO}_2\text{H}$	Me	4-OMe	H	4'-Cl	H
	43	H	$(\text{CH}_2)_2\text{CO}_2\text{H}$	Me	4-Cl	H	4'-Cl	H
5	44	H	$(\text{CH}_2)_2\text{CO}_2\text{H}$	Me	4-Cl	6-Cl	4'-CF ₃	H
	45	H	$(\text{CH}_2)_3\text{CO}_2\text{H}$	Me	5-OMe	4-Cl	H	H
	46	same as 2 to 16 with R ² being $(\text{CH}_2)_3\text{COOH}$						
	47	H	$\text{CH}(\text{Me})\text{CH}_2\text{CO}_2\text{H}$	Me	5-OMe	4-Cl	H	H
	48	same as 2 to 16 with R ² being $\text{CH}(\text{Me})\text{CH}_2\text{COOH}$						
10	49	H	$\text{CH}_2-\text{CH}(\text{Me})-\text{COOH}$	Me	5-OMe	H	4'-Cl	H
	50	same as 2 to 16 with R ² being $\text{CH}_2-\text{CH}(\text{Me})\text{COOH}$						
	51	H	$\text{CH}(\text{Me})(\text{CH}_2)_2-\text{COOH}$	Me	5-OMe	H	4'-Cl	H
	52	same as 2 to 16 with R ² being $\text{CH}(\text{Me})(\text{CH}_2)_2-\text{COOH}$						
	53	H	$\text{CH}_2-\text{CH}(\text{Me})\text{CH}_2\text{COOH}$	Me	5-OMe	H	4'-Cl	H
15	54	same as 2 to 16 with R ² being $\text{CH}_2-\underset{\text{Me}}{\text{CH}}-\text{CH}_2-\text{COOH}$						
	55	H	$\text{CH}_2\text{CH}_2\text{CH}(\text{Me})-\text{COOH}$	Me	5-OMe	H	4'-Cl	H
	56	same as 2 to 16 with R ² being $(\text{CH}_2)_2-\text{CH}(\text{Me})\text{COOH}$						
	57	H	$\text{CH}_2-\text{C}(\text{Me})_2-\text{COOH}$	Me	5-OMe	H	4'-Cl	H
20	58	same as 2 to 16 with R ² being $\text{CH}_2-\text{C}(\text{Me})_2-\text{COOH}$						
	59	H	$\text{CH}_2-\text{C}(\text{Me})_2\text{CH}_2\text{COOH}$	Me	5-OMe	H	4'-Cl	H
	60	same as 2 to 16 with R ² being $\text{CH}_2-\text{C}(\text{Me})_2-\text{CH}_2-\text{COOH}$						
	61	H	$(\text{CH}_2)_2-\text{C}(\text{Me})_2-\text{COOH}$	Me	5-OMe	H	4'-Cl	H
25	62	same as 2 to 16 with R ² being $(\text{CH}_2)_2-\text{C}(\text{Me})_2-\text{COOH}$						
	63	H	$\text{CH}_2-\text{OCH}_2\text{COOH}$	Me	5-OMe	H	4'-Cl	H
	64	same as 2 to 16 with R ² being $\text{CH}_2-\text{OCH}_2\text{COOH}$						
	65	H	$\text{CH}_2-\text{S}-\text{CH}_2\text{CO}_2\text{H}$	Me	5-OMe	H	4'-Cl	H
30	66	H	$\text{CH}_2-\underset{\text{O}}{\text{S}}-\text{CH}_2\text{CO}_2\text{H}$	Me	5-OMe	H	4'-Cl	H

0166591

2893P/1046A

2894P/1039A

- 39 -

17102IA

67	H	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_2\text{S}-\text{CH}_2\text{CO}_2\text{H} \\ \downarrow \\ \text{O} \end{array}$	Me	5-OMe	H	4'Cl	H
68	same as 2 to 16 with R^2 being $\text{CH}_2\text{-S-CH}_2\text{CO}_2\text{H}$						
5 69	same as 2 to 16 with R^2 being $\text{CH}_2\text{-S-CH}_2\text{CO}_2\text{H}$						
70	H	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}(\text{CH}_3)_2\text{CH}_2\text{CO}_2\text{H} \\ \downarrow \\ \text{O} \end{array}$	Me	5-OMe	H	4'Cl	H
71	H	$\begin{array}{c} \text{CH}_2\text{N-CHCH}_2\text{CO}_2\text{H} \\ \\ \text{CN} \end{array}$	Me	5-OMe	H	4'Cl	H
10 72	same as 2 to 16 with R^2 being $\text{CH}_2\text{-N-CH}_2\text{CO}_2\text{H}$						
73	same as 2 to 16 with R^2 being $\text{CH}(\text{CH}_3)_2\text{COOH}$						
74	same as 2 to 16 with R^2 being $\text{CH}(\text{CH}_3)\text{C}(\text{CH}_3)_2\text{CH}_2\text{COOH}$						

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2893P/1046A

2894P/1039A

- 40 -

171021A

Specific Examples of the Formula I compounds are the following, all but the first being novel:

- 5 3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]
 propionic acid;
- 3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]
 propionic acid;
- 10 3-[1-(4-chlorobenzyl)-3,4-dimethylindol-2-yl]
 propionic acid;
- 4-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]
 butanoic acid;
- 15 3-[1-(4-chlorobenzyl)-3-methyl-5-hydroxyindol-2-yl]
 propionic acid;
- 3-[1-(4-chlorobenzyl)-3-methylindol-2-yl]propionic
20 acid;
- 3-[1-(4-methylthiobenzyl)-3-methyl-5-methoxyindol-2-
 yl]propionic acid;
- 25 3-[1-(4-methylthiobenzyl)-3-methyl-5-fluoroindol-2-yl]
 propionic acid;
- 3-[1-(4-methylsulfinylbenzyl)-3-methyl-5-methoxyindol-
 2-yl]propionic acid;
- 30 4-[1-(4-methylthiobenzyl)-3-methyl-5-methoxyindol-
 2-yl]butanoic acid;

0166591

2893P/1046A

2894P/1039A

- 41 -

171021A

4-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]
butanoic acid;

5 1-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]
methoxy acetic acid;

3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-
2,2-dimethylpropanoic acid;

10 3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-
yl]-3-methylpropanoic acid;

3-methyl-4-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-
indol-2-yl]butanoic acid;

15 3-methyl-4-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-
indol-2-yl]butanoic acid;

20 3-[1-(4-chlorobenzyl-3-methyl-5-fluoro-2-indolyl)-2,2-
dimethyl propanoic acid.

Further examples include:

25 4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)-
2,4,3,3-tetramethyl butanoic acid;

4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)-
4,3,3-trimethyl butanoic acid;

30 4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)-
2,2,3-trimethyl butanoic acid;

0166591

2893P/1046A

2894P/1039A

- 42 -

171021A

- 4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-
2,3,3-trimethyl butanoic acid;
- 5 4-[1-(4-chlorobenzyl-5-methoxy-3-methyl-1H-indol-2-yl)]-
2,2,3-trimethyl butanoic acid;
- 4-[1-(4-chlorobenzyl-5-ethoxy-3-methyl-1H-indol-2-yl)]-
2,2,3-trimethyl butanoic acid;
- 10 4-[1-(4-chlorobenzyl-5-chloro-3-methyl-1H-indol-2-yl)]-
2,2,3-trimethyl butanoic acid;
- 15 4-[1-(4-chlorobenzyl-3-methyl-5-trifluoromethyl-1H-
indol-2-yl)]-2,4,3,3-tetramethyl butanoic acid;
- 4-[1-(4-chlorobenzyl-3-methyl-5-trifluoromethylthio-
1H-indol-2-yl)]-2,4,3,3-tetramethyl butanoic acid;
- 20 3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-
2,2,3-trimethyl propanoic acid;
- 3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-
2,3,3-trimethyl propanoic acid;
- 25 3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-
2,2,3,3-tetramethyl propanoic acid;
- 3-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-
yl]-2,2,3-trimethyl propanoic acid;
- 30 3-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-1H-indol-2-
yl]-2,2,3-trimethyl propanoic acid;

2893P/1046A

2894P/1039A

- 43 -

171021A

3-[1-(4-chlorobenzyl)-5-chloro-3-methyl-1H-indol-2-yl]-2,2,3-trimethyl propanoic acid;

5 3-(1-p-chlorobenzyl-3-methyl-5-methoxyindol-2-yl)-2,2-diethyl propanoic acid;

3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2,2-diethyl propanoic acid;

10 3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2-ethyl propanoic acid;

3-[1-(4-chlorobenzyl)-3-ethyl-5-fluoroindol-2-yl]-3-methyl propanoic acid; and

15

3-[1-(4-chlorobenzyl-3-methyl-5-methoxy-2-indolyl)]pentanoic acid.

20 In those instances when asymmetric centers are present, more than one stereoisomer is possible, and all possible isomeric forms are deemed to be included within the planar structural representations shown. Optically active (R) and (S) isomers may be resolved using conventional techniques known to the
25 skilled artisan.

The prostaglandin antagonist properties of the compounds of the present invention can be demonstrated by a number of biological assays, one of which, inhibition of platelet aggregation, is
30 described below.

2893P/1046A

2894P/1039A

- 44 -

171021A

Inhibition of Induced Threshold Aggregation of Human Platelets

Human platelet rich plasma (PRP) is prepared from venous blood of male volunteers who have taken
5 no medication for ten days prior to test. Blood is transferred into plastic centrifuge tubes containing 3.8% Trisodium Citrate in 0.9% NaCl (in a ratio of blood to anticoagulant of 9:1), mixed by gentle inversion, and centrifuged at room temperature for
10 ten minutes at 116 g. The supernatant (PRP) is transferred into plastic tubes. Platelet poor plasma (PPP) is obtained by centrifuging the residual blood cells at 4000 g for ten minutes. PRP is left to stand at least one half hour prior to testing.

15 Platelet Aggregation is measured using a Payton Aggregometer and Recorder. Following calibration of the instrument, a cuvette containing PRP (225 microliters) is incubated for three minutes at 37°C. Drug vehicle (control), or a drug concentra-
20 tion is then added in a volume of 0.5 microliter. After one minute, the aggregating agent (U44069, 9,11-dideoxy-9 α ,11 α -epoxymethano PGF₂) is added to the cuvette in a volume of 25 microliters. Recording is continued until the maximal response is obtained.

25 The threshold (approximately 20 - 30% of maximum) aggregation concentration of the agonist to be used is first determined in the presence of the drug vehicle (control). Test compounds are then assayed at 10 or 30 micrograms/ml initially, and if
30 active, are further tested in order to determine the concentration range at which 20-80% of the threshold aggregatory response is inhibited. All drugs are dissolved in dimethylsulfoxide.

2893P/1046A

2894P/1039A

- 45 -

171021A

The height of the aggregation response (measured in divisions of the recorder paper, 1 division = 2.5 mm) in the presence of the drug is recorded, and calculated as percent inhibition of the mean height of the control threshold responses. The IC_{50} (drug concentration which inhibits 50% of the aggregatory response) is obtained by regression analysis.

Compounds of Formula I or Ia can be tested using the following assay to determine their mammalian leukotriene biosynthesis inhibiting activity.

Rat Peritoneal Polymorphonuclear (PMN)

15

Leukocyte Assay

Rats under ether anesthesia are injected (i.p.) with 8 ml of a suspension of sodium caseinate (6 grams in ca. 50 ml water). After 15-24 hr. the rats are sacrificed (CO_2) and the cells from the peritoneal cavity are recovered by lavage with 20 ml of buffer (Eagles MEM containing 30 mM HEPES adjusted to pH 7.4 with NaOH). The cells are pelleted (350 x g, 5 min.), resuspended in buffer with vigorous shaking, filtered, through lens paper, recentrifuged and finally suspended in buffer at a concentration of 10 cells/ml. A 500 μ l aliquot of PMN suspension and test compound are preincubated for 2 minutes at 37°C, followed by the addition of 10 μ M A-23187. The suspension is stirred for an additional 4 minutes then bioassayed for LTB_4 content by adding an aliquot to a second 500 μ l portion of the PMN at 37°C. The LTB_4 produced in the first incubation

causes aggregation of the second PMN, which is measured as a change in light transmission. The size of the assay aliquot is chosen to give a submaximal transmission change (usually -70%) for the untreated control. The percentage inhibition of LTB_4 formation is calculated from the ratio of transmission change in the sample to the transmission change in the compound-free control.

The cytoprotective activity of a compound may be observed in both animals and man by noting the increased resistance of the gastrointestinal mucosa to the noxious effects of strong irritants, for example, the ulcerogenic effects of aspirin or indomethacin. In addition to lessening the effect of non-steroidal anti-inflammatory drugs on the gastrointestinal tract, animal studies show that cytoprotective compounds will prevent gastric lesions induced by oral administration of strong acids, strong bases, ethanol, hypertonic saline solutions and the like.

Two assays can be used to measure cytoprotective ability. These assays are: (A) an ethanol-induced lesion assay and (B) an indomethacin-induced ulcer assay.

A. Ethanol-Induced Gastric Ulcer Assay

Twenty-four hour fasted Sprague-Dawley (S.D.) rats are perorally (p.o.) dosed with 1.0 ml absolute ethanol. Fifteen to thirty minutes prior to ethanol administration, groups of rats each receive either an aqueous vehicle (aqueous methylcellulose 5% wt.) or

2893P/1046A

2894P/1039A

- 47 -

171021A

the test compound at various doses perorally. One hour later, the animals are sacrificed and stomach mucosae are examined for resulting lesions.

5 B. Indomethacin-Induced Ulcer Assay

Indomethacin, 10 mg/kg p.o., is used to induce ulcers in 24 hour fasted S.D. rats. Fifteen minutes prior to indomethacin administration, groups of rats each receive either an aqueous vehicle (5% by weight methylcellulose) or the test compound at various doses perorally. Four hours later the animals are sacrificed and stomach mucosae are examined for resulting ulcers.

10 The magnitude of a prophylactic or therapeutic dose of a compound of Formula I or Ia will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I or Ia and its route of administration. In general, the daily dose range for anti-asthmatic, anti-allergic, anti-inflammatory, or anti-thrombotic use lies within the range of from about 0.01 mg to about 100 mg per kg body weight of a mammal.

15 The exact amount of a compound of Formula I or Ia to be used as a cytoprotective agent will depend on, inter alia, whether it is being administered to heal damaged cells or to avoid future damage, on the nature of the damaged cells (e.g., gastro-intestinal ulcerations vs. nephrotic necrosis), and on the nature of the causative agent. An example of use of a compound of Formula I or Ia to avoid

2893P/1046A

2894P/1039A

- 48 -

171021A

future damage is co-administration with a non-steroidal anti-inflammatory drug (for example, indomethacin).

5 The effective daily dosage level for
compounds of Formulae I or Ia inducing cytoprotection
in mammals, especially humans, will generally range
from about 0.002 mg/kg to about 100 mg/kg, preferably
from about 0.02 mg/kg to about 30 mg/kg. The dosage
may be administered in single or divided individual
10 doses.

Any suitable route of administration may be
employed for providing a mammal, especially a human
with an effective dosage of a compound of Formula I
or Ia. For example, oral, rectal, transdermal,
15 parenteral, intramuscular, intravenous and the like
may be employed. Dosage forms include tablets,
troches, dispersions, suspensions, solutions,
capsules and the like.

The pharmaceutical compositions of the
20 present invention comprise a compound of Formula I or
Ia as an active ingredient or a pharmaceutically
acceptable salt thereof, and may also contain a
pharmaceutically acceptable carrier and optionally
other therapeutic ingredients. The term "pharma-
25 ceutically acceptable salts" refers to salts prepared
from pharmaceutically acceptable non-toxic bases
including inorganic bases and organic bases. Salts
derived from inorganic bases include sodium,
potassium, lithium, ammonium, calcium, magnesium,
30 ferrous, zinc, copper, manganous, aluminum, ferric,
manganic salts and the like. Particularly preferred
are the ammonium, potassium, sodium, calcium and

2893P/1046A

2894P/1039A

- 49 -

17102IA

magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. The compositions include compositions suitable for oral, rectal, ophthalmic, pulmonary, nasal, dermal, topical or parenteral (including subcutaneous, intramuscular and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For use where a composition for intravenous administration is employed, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use is from about 0.01 mg to about 20 mg (preferably from about 0.1 mg to about 10 mg) of a compound of Formula I or Ia per kg of body weight per day and for cytoprotective use from about 0.002 mg to about 100 mg (preferably from about 0.02 mg to about 30 mg and more preferably from about 0.1 mg to about

2893P/1046A

2894P/1039A

- 50 -

171021A

10 mg) of a compound of Formula I or Ia per kg of body weight per day. In the case where an oral composition is employed, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use is, e.g. from about 1 to about 100 mg of a
5 compound of Formula I or Ia per kg of body weight per day, preferably from about 5 mg to about 40 mg per kg and for cytoprotective use from about 0.01 mg to about 100 mg (preferably from about 0.1 mg to about
10 30mg and were preferably from about 0.1 mg to about 10 mg) of a compound of Formula I or Ia per kg of body weight per day.

For administration by inhalation, the compounds of the present invention are conveniently
15 delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser. The preferred composition for inhalation is a powder which may be formulated as a cartridge from which the powder composition may be inhaled with the aid of a
20 suitable device. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

In practical use, a compound of Formula I or Ia can be combined as the active ingredient in
25 intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or intravenous. In
30 preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water glycols, oils, alcohols,

2893P/1046A

2894P/1039A

- 51 -

17102IA

flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques.

In addition to the common dosage forms set out above, the compounds of Formula I or Ia may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719, the disclosure of which is hereby incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration and by inhalation in the case of asthma therapy may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association

2893P/1046A

2894P/1039A

- 52 -

171021A

the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 25 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 25 to about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I or Ia:

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0166591

2893P/1046A

2894P/1039A

- 53 -

171021A

	<u>Injectable Suspension</u>	<u>mg/ml</u>
	Compound of Formula I or Ia	2.0
	Methylcellulose	5.0
	Tween 80	0.5
5	Benzyl alcohol	9.0
	Methyl paraben	1.8
	Propyl paraben	0.2
	Water for injection to a total volume of 1 ml	
10	<u>Tablet</u>	<u>mg/tablet</u>
	Compound of Formula I or Ia	25.0
	Microcrystalline Cellulose	325.0
	Providone	14.0
	Microcrystalline Cellulose	90.0
15	Pregelatinized Starch	43.5
	Magnesium Stearate	<u>2-2.5</u>
		500
	<u>Capsule</u>	<u>mg/capsule</u>
20	Compound of Formula I or Ia	25.0
	Lactose Powder	573.5
	Magnesium Stearate	<u>1-1.5</u>
		600

- 25 In addition to the compounds of Formula I or Ia, the pharmaceutical compositions of the present invention can also contain other active ingredients, such as non-steroidal anti-inflammatory drugs (NSAIDs), peripheral analgesic agents such as
- 30 zomepirac, diflunisal and the like, cyclooxygenase inhibitors, leukotriene antagonists, leukotriene biosynthesis inhibitors, H₂-receptor antagonists,

2893P/1046A

2894P/1039A

- 54 -

171021A

antihistaminic agents, prostaglandin antagonists, ACE inhibitors, and thromboxane synthetase inhibitors.

The weight ratio of the compound of the Formula I or Ia to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I or Ia is combined with a second active ingredient the weight ratio of the compound of the Formula I or Ia to the second ingredient will generally range from about 1000:1 to about 1:1000, preferably from 200:1 to 1:200. Combinations of a compound of the Formula I or Ia and other active ingredients will generally be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

NSAIDs can be characterized into five groups:

- (1) the propionic acid derivatives;
 - (2) the acetic acid derivatives;
 - (3) the fenamic acid derivatives;
 - (4) the biphenylcarboxylic acid derivatives;
- and
- (5) the oxicams

or a pharmaceutically acceptable salt thereof.

The propionic acid derivatives which may be used comprise: ibuprofen, ibuprofen aluminum, indoprofen, ketoprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tiroxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic

2893P/1046A

2894P/1039A

- 55 -

171021A

acid. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be included in this group.

5 Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-\text{CH}(\text{CH}_3)\text{COOH}$ or $-\text{CH}_2\text{CH}_2\text{COOH}$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, 10 e.g., $-\text{CH}(\text{CH}_3)\text{COO}^-\text{Na}^+$ or $-\text{CH}_2\text{CH}_2\text{COO}^-\text{Na}^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

 The acetic acid derivatives which may be 15 used comprise: indomethacin, which is a preferred NSAID, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acetaminophen, fentiazac, clidanac, oxpinac, and fenclozic acid. 20 Structurally related acetic acid derivatives having similar analgesic and antiinflammatory properties are also intended to be encompassed by this group.

 Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti- 25 inflammatory drugs having a free $-\text{CH}_2\text{COOH}$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-\text{CH}_2\text{COO}^-\text{Na}^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

30 The fenamic acid derivatives which may be used comprise: mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid.

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2893P/1046A

2894P/1039A

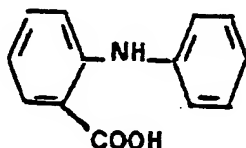
- 56 -

171021A

Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "fenamic acid derivatives" as defined
5 herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:

10

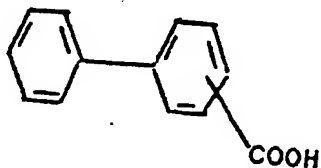


which can bear a variety of substituents and in which the free -COOH group can be in the form of a
15 pharmaceutically acceptable salt group, e.g., -COO⁻Na⁺.

The biphenylcarboxylic acid derivatives which can be used comprise: diflunisal and flufenisal. Structurally related biphenylcarboxylic
20 acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "biphenylcarboxylic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the
25 basic structure:

30



2893P/1046A

2894P/1039A

- 57 -

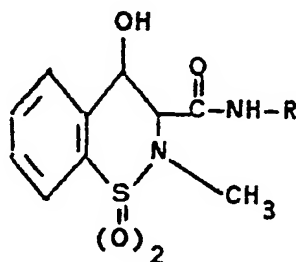
171021A

which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., -COO⁻Na⁺.

5 The oxicams which can be used in the present invention comprise: piroxicam, sudoxicam, isoxicam and 4-hydroxyl-1,2-benzothiazine 1,1-dioxide 4-(N-phenyl)-carboxamide. Structurally related oxicams having similar analgesic and anti-inflammatory
10 properties are also intended to be encompassed by this group.

Thus, "oxicams" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula:

15



20

wherein R is an aryl or heteroaryl ring system.

The following NSAIDs may also be used:

25 acemetacin, alminoprofen, amfenac sodium, aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate, benzydamine, beprozin, broperamole, bufezolac, carprofen, cinmetacin, ciproquazone, clidanac, cloximate, dazidamine, deboxamet,
30 delmetacin, detomidine, dexindoprofen, diacerein, di-fisalamine, difenpyramide, emorfazone, enfenamic acid, enolicam, epirizole, etersalate, etodolac,

0166591

2893P/1046A

2894P/1039A

- 58 -

171021A

etofenamate, fanetizole mesylate, fenclofenac,
fenclorac, fendosal, fenflumizole, fentiazac,
feprazone, floctafenine, flunixin, flunoxaprofen,
fluproquazone, fopirtoline, fosfosal, furclopofen,
5 furofenac, glucametacin, guaimesal, ibuprofen,
isofezolac, isonixim, isoprofen, isoxepac, isoxicam,
lefetamine HCl, leflunomide, lofemizole, lonazolac
calcium, lotifazole, loxoprofen, lysin clonixinate,
meclofenamate sodium, meseclazone, miroprofen,
10 nabumetone, nictindole, nimesulide, orpanoxin,
oxametacin, oxapadol, oxaprozin, perisoxal citrate,
pimeprofen, pimetacin, piprofen, pirazolac,
pirfenidone, pirprofen, pranoprofen, proglumetacin
maleate, proquazone, pyridoxiprofen, sudoxicam,
15 suprofen, talmetacin, talniflumate, tenoxicam,
thiazolinobutazone, thielavin B, tiaprofenic acid,
tiaramide HCl, tiflamizole, timegadine, tioxaprofen,
tolfenamic acid, tolpadol, tryptamid, ufenamate, and
zidometacin.

20 The following NSAIDs, designated by company
code number, may also be used:

480156S, AA861, AD1491, AD1590, AFP802, AFP860,
AHR6293, AI77B, AP504, AU8001, BAYo8276, BPPC,
BW540C, BW755C, CHINOIN 127, CN100, CO893XX, CPP,
25 D10242, DKA9, DV17, EB382, EGYT2829, EL508, F1044,
FZ, GP53633, GP650, GV3658, HG/3, ITC1, ITF, ITF182,
KB1043, KC8973, KCNTEI6090, KME4, LA2851, LT696,
LU20884, M7074, MED15, MG18311, MR714, MR897, MY309,
NO164, ONO3144, PR823, PV102, PV108, QZ16, R830,
30 RS2131, RU16029, RU26559, RUB265, SCR152, SH440,
SIR133, SIR136, SIR92, SPAS510, SQ27239, ST281,
SX1032, SY6001, SaH46798, TA60, TAI901, TEI615,

2893P/1046A

2894P/1039A

- 59 -

171021A

TVX2706, TVX960, TZI615, U60257, UR2310, WY23205,
WY41770, YMO9561, YM13162, YS1033, and ZK31945.

Finally, NSAIDs which may also be used
include the salicylates, specifically aspirin, and
5 the phenylbutazones, and pharmaceutically acceptable
salts thereof.

Pharmaceutical compositions comprising the
Formula I or Ia compounds may also contain other
inhibitors of the biosynthesis of the leukotrienes
10 such as are disclosed in EP 138,481 (April 24, 1985),
EP 115,394 (August 8, 1984), EP 136,893 (April 10,
1985), and EP 140,709 (May 8, 1985), which are hereby
incorporated herein by reference.

The compounds of the Formula I or Ia may
15 also be used in combination with leukotriene
antagonists such as those disclosed in EP 106,565
(April 25, 1984) and EP 104,885 (April 4, 1984),
which are hereby incorporated herein by reference and
others known in the art such as those disclosed in
20 European Patent Application Nos. 56,172 and 61,800;
and in U.K. Patent Specification No. 2,058,785, which
are hereby incorporated herein by reference.

Pharmaceutical compositions comprising the
Formula I or Ia compounds may also contain as the
25 second active ingredient, antihistaminic agents such
as benadryl, dramamine, histadyl, phenergan and the
like. Alternatively, they may include other
prostaglandin antagonists such as those disclosed in
European Patent Application 11,067 (May 28, 1980) or
30 other thromboxane antagonists such as those disclosed
in U.S. 4,237,160. They may also contain histidine

2893P/1046A

2894P/1039A

- 60 -

171021A

decarboxyase inhibitors such as α -fluoromethyl-histidine, described in U.S. 4,325,961. The compounds of the Formula I may also be advantageously combined with an H_1 or H_2 -receptor antagonist, such as for instance cimetidine, ranitidine, 5 terfenadine, famotidine, aminothiadiazoles disclosed in EP 40,696 (December 2, 1981) and like compounds, such as those disclosed in U.S. Patent Nos. 4,283,408; 4,362,736; 4,394,508; and a pending 10 application, U.S.S.N. 301,616, filed September 14, 1981. The pharmaceutical compositions may also contain a K^+/H^+ ATPase inhibitor such as omeprazole, disclosed in U.S. Pat. 4,255,431, and the like. Each of the references referred to in this 15 paragraph is hereby incorporated herein by reference.

When the second active ingredient in compositions of this invention is a thromboxane synthetase inhibitor, such inhibitor can be as described in UK 2,038,821 (e.g., UK 37248 and 20 dazoxiben hydrochloride), U.S.P. 4,217,357 (e.g., UK 34787), U.S.P. 4,444,775 (e.g., CGS 13080), U.S.P. 4,226,878 (e.g., ONO 046), U.S.P. 4,495,357 (e.g., U63557A) U.S.P. 4,273,782 (e.g., UK-38485), or EP 98,690 (e.g., CV-4151).

25 An embodiment of the invention is a cardiovascular composition useful for treating arterial thrombosis which comprises an antithrombotic compound of the Formula I or Ia.

30 A further embodiment of the invention is a cardiovascular composition useful for treating

2893P/1046A

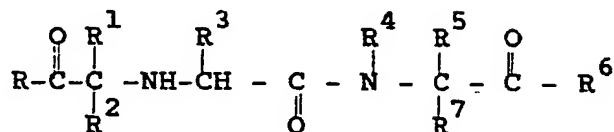
2894P/1039A

- 61 -

171021A

arterial thrombosis which comprises: (1) the antithrombotic Formula I or Ia compound defined above; and, (ii) an angiotensin converting enzyme (ACE) inhibitor compound which is a member of the group: carboxyalkyl dipeptide derivatives; captopril [1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline]; 2-[N-(S)-1-ethoxycarbonyl-3-phenylpropyl]-S-alanyl]-cis,endo-2-azabicyclo[3.3.0]octane-3(S)-carboxylic acid; N-((S)-1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-N-(2-indanyl)-glycine; 1-(N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl)-cis,syn-octahydro-(H-indole-2-S)-carboxylic acid; 2-(N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl)-1,2,3,4-tetrahydro-iso-isoquinoline-3(S)-carboxylic acid; and, 1-carboxymethyl-3(S)-(1(S)-ethoxycarbonyl-3-phenylpropylamino)-2,3,4,5-tetrahydro-1H[1]-benzazepine-2-one.

In particular the class of ACE inhibitors which have been found to have a potentiating effect when used in combination with the Formula I or Ia compounds are those disclosed in U.S. Patent 4,374,829, which also discloses methods for their preparation and which patent is incorporated herein by reference and which compounds are generally represented by the Formula XI:



30

XI

wherein

2893P/1046A

2894P/1039A

- 62 -

17102IA

- R and R⁶ are the same or different and are hydroxy,
lower C₁-C₈ alkoxy;
lower C₁-C₈ alkenoxy;
dilower C₁-C₈ alkylamino lower C₁-C₈
5 alkoxy (dimethylaminoethoxy);
acylamino lower C₁-C₈ alkoxy (acetyl-
aminoethoxy);
acyloxy lower C₁-C₈ alkoxy (pivaloyloxy-
methoxy);
10 aryloxy, wherein the aryl is C₆ or C₁₀
such as phenoxy;
arlower C₁-C₈ alkoxy, such as benzyloxy;
substituted aryloxy or substituted
arlower-C₁-C₈ alkoxy wherein the aryl is
15 C₆ or C₁₀ and the substituent is methyl,
halo or methoxy;
amino;
lower C₁-C₈ alkylamino;
dilower C₁-C₈ alkylamino;
20 hydroxyamino;
arlower C₁-C₈ alkylamino wherein the
aryl group is C₆-C₁₀ such as benzylamino;
R¹ is hydrogen;
hydrocarbon of from 1 to 20 carbon atoms
25 which include branched and unsaturated
(such as allyl) groups;
C₃-C₁₀ cycloalkyl;
substituted lower C₁-C₈ alkyl wherein
the substituent can be halo, hydroxy,
30 lower C₁-C₈ alkoxy, aryloxy wherein
the aryl is C₆-C₁₀ such as phenoxy,

2893P/1046A

2894P/1039A

- 63 -

17102IA

amino, dilower C_1-C_8 alkylamino,
acylamino such as acetamido and
benzamido, arylamino wherein the aryl
is C_6 or C_{10} , guanidino,
5 imidazolyl, indolyl, mercapto, lower
 C_{1-8} alkylthio, arylthio wherein the
aryl is C_6 or C_{10} such as
phenylthio, carboxy or carboxamido,
carbolower C_{1-8} alkoxy;
10 aryl of C_6-C_{10} such as phenyl or
naphthyl;
substituted aryl of C_6-C_{10} such as
phenyl wherein the substituent is lower
 C_1-C_8 alkyl, lower C_1-C_8 alkoxy
15 or halo,
unsubstituted or substituted arloweralkyl,
arloweralkenyl, heteroarlower alkyl, or
heteroarlower alkenyl, wherein aryl
groups are C_6 or C_{10} , the alkyl
20 groups are C_2-C_8 , and the
heteroatoms are one of O, N or S and
the the substituent(s) is halo, dihalo,
lower C_1-C_8 alkyl, hydroxy, lower
 C_1-C_8 alkoxy, amino, aminomethyl,
25 acylamino (acetylamino or benzoylamino)
dilower C_1-C_8 alkylamino, lower
 C_1-C_8 alkylamino, carboxyl,
halolower C_1-C_8 alkyl, cyano or
sulfonamido;
30 arlower C_1-C_8 alkyl or heteroarlower
 C_1-C_8 alkyl wherein the aryl group
is C_6 or C_{10} and the heteroatom is

2893P/1046A

2894P/1039A

- 64 -

171021A

one of O, N or S, substituted on the
alkyl portion by amino or acylamino
(acetylamino or benzoylamino);

- R^2 and R^7 are the same or different and are
- 5 hydrogen or lower C_1-C_8 alkyl;
- R^3 is hydrogen, lower C_1-C_8 alkyl, phenyl
lower C_1-C_8 alkyl, aminomethyl phenyl
lower C_1-C_8 alkyl, hydroxy phenyl lower
10 C_1-C_8 alkyl, hydroxy lower C_1-C_8
alkyl, acylamino lower C_1-C_8 alkyl (such
as benzoylamino lower C_1-C_8 alkyl,
acetylamino lower C_1-C_8 alkyl), amino
lower C_1-C_8 alkyl, dimethylamino lower
 C_1-C_8 alkyl, halo lower C_1-C_8 alkyl,
15 guanidino lower C_1-C_8 alkyl, imidazolyl
lower C_1-C_8 alkyl, indolyl lower
 C_1-C_8 alkyl, mercapto lower C_1-C_8
alkyl, lower C_1-C_8 alkyl thio lower
 C_1-C_8 alkyl;
- 20 R^4 is hydrogen or lower C_1-C_8 alkyl;
- R^5 is hydrogen, lower C_1-C_8 alkyl, phenyl,
phenyl lower C_1-C_8 alkyl, hydroxy phenyl
lower C_1-C_8 alkyl, hydroxy lower
 C_1-C_8 alkyl, amino lower C_1-C_8
25 alkyl, guanidino lower C_1-C_8 alkyl,
imidazolyl lower C_1-C_8 alkyl, indolyl
lower C_1-C_8 alkyl, mercapto lower
 C_1-C_8 alkyl or lower C_1-C_8 alkyl
thio lower C_1-C_8 alkyl; or,
- 30 R^4 and R^5 may be connected together to form an
alkylene bridge of from 2 to 4 carbon atoms,
an alkylene bridge of from 2 to 3 carbon

2893P/1046A

2894P/1039A

- 65 -

171021A

atoms and one sulfur atom, an alkylene
bridge of from 3 to 4 carbon atoms
containing a double bond or an alkylene
bridge as above substituted with hydroxy,
5 lower C₁-C₈ alkoxy, lower C₁-C₈
alkyl or dilower C₁₋₈ alkyl;
and, the pharmaceutically acceptable salts thereof.

Preferred ACE inhibitor compounds of Formula
10 VI are those wherein:
R and R⁶ can each independently be hydroxy, lower
alkoxy, lower alkenoxy, arloweralkyloxy,
amino, diloweralkylamino lower alkoxy,
acylamino lower alkoxy or acyloxy lower
15 alkoxy;
R¹ is hydrogen,
alkyl of from 1 to 20 carbon atoms,
including branched, cyclic and unsaturated
alkyl groups;
20 substituted lower alkyl wherein the
substituent is halo, hydroxy, lower alkoxy,
aryloxy, amino, loweralkylamino,
diloweralkylamino, acylamino, arylamino,
~~guanidino, imidazolyl, indolyl, mercapto,~~
25 loweralkylthio, arylthio, carboxy,
carboxamido or carbolower alkoxy;
phenyl;
substituted phenyl wherein the substituent
is lower alkyl, lower alkoxy or halo;
30 arloweralkyl or heteroarylloweralkyl
arloweralkenyl or heteroarloweralkenyl,
substituted arloweralkyl, substituted

2893P/1046A

2894P/1039A

- 66 -

171021A

heteroaryl lower alkyl, substituted
aryl lower alkenyl or substituted
heteroaryl lower alkenyl;
wherein the substituent is halo or dihalo
5 lower alkyl, hydroxy, lower alkoxy, amino,
aminomethyl, acylamino, dialkylamino,
lower alkylamino, carboxyl, halo alkyl, cyano
or sulfonamido;
aryl lower alkyl or heteroaryl lower alkyl
10 substituted on the alkyl portion by amino or
acylamino;
R² and R⁷ are hydrogen;
R³ is lower alkyl, amino lower alkyl, imidazolyl,
lower alkyl, halo lower alkyl;
15 R⁴ and R⁵ are joined to form an alkylene bridge
of from 2 to 4 carbon atoms or an alkylene
bridge of from 2 or 3 carbon atoms and one
sulfur atom or an alkylene bridge of from 2
to 3 carbon atoms and one sulfur atom or an
20 alkylene bridge of from 3 to 4 carbon atoms
containing a double bond or an alkylene
bridge of from 3 to 4 carbon atoms contain-
ing a double bond or an alkylene bridge as
above substituted with hydroxy, lower alkoxy
25 or lower alkyl;
or the pharmaceutically acceptable salts thereof
wherein said aryl is a member selected from the group
consisting of phenyl or naphthyl and said heteroaryl
is a member selected from the group consisting of
30 pyridyl, thienyl, furyl, indolyl, benzthienyl,
imidazolyl, or thiazolyl.

2893P/1046A

2894P/1039A

- 67 -

17102IA

More preferred are those antihypertensive compounds of Formula VI wherein:

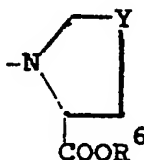
R and R⁶ can each independently be hydroxy, lower alkoxy, lower alkenoxy, arloweralkyloxy, amino, diloweralkylamino lower alkoxy, acylamino lower alkoxy or acyloxy lower alkoxy;

R¹ is alkyl having from 1-8 carbon atoms, substituted lower alkyl wherein the alkyl group has 1-5 carbon atoms and the substituent is amino, arylthio, aryloxy or arylamino, aralkyl or heteroaralkyl wherein the alkyl portion has 1-3 carbon atoms, substituted aralkyl or heteroaralkyl wherein the alkyl groups have 1-3 carbon atoms and the substituent(s) is halo, dihalo, amino, aminoalkyl, hydroxy, lower alkoxy or lower alkyl;

R² and R⁷ are hydrogen;

R³ is lower alkyl or amino lower alkyl;

R⁴ and R⁵ can be joined together through the carbon and nitrogen atoms to which they are attached to form a ring of the formula:



wherein Y is CH₂, S, or CH-OCH₃ or the pharmaceutically acceptable salts thereof wherein said aryl is a member selected from

2893P/1046A

2894P/1039A

- 68 -

171021A

the group consisting of phenyl or naphthyl
and said heteroaryl is a member selected
from the group consisting of pyridyl,
thienyl, furyl, indolyl, benzthienyl,
5 imidazolyl or thiazolyl.

Still more preferred antihypertensive
compounds of Formula VI are those wherein:
R and R⁶ can each independently be hydroxy, lower
10 alkoxy, aralkyloxy;
R² and R⁷ are hydrogen;
R³ is methyl, aminoloweralkyl;
R⁴ and R⁵ are joined through the carbon and
nitrogen atoms to form proline,
15 4-thiaproline or 4-methoxyproline and;
R¹ is alkyl having from 1-8 carbon atoms,
substituted lower alkyl wherein the alkyl
group has 1-5 carbon atoms and the
substituent is amino, arylthio or aryloxy,
20 aralkyl or heteroaralkyl wherein the alkyl
portion has 1-3 carbon atoms, substituted
aralkyl or heteroaralkyl wherein the alkyl
groups have 1-3 carbon atoms and the
substituent(s) is halo, dihalo, amino,
25 aminoalkyl, hydroxy, lower alkoxy or lower
alkyl;
and the pharmaceutically acceptable salts thereof
wherein said aryl is a member selected from the group
consisting of phenyl or naphthyl and said heteroaryl
30 is a member selected from the group consisting of
pyridyl, thienyl, furyl, indolyl, benzthienyl,
imidazolyl or thiazolyl.

2893P/1046A

2894P/1039A

- 69 -

171021A

Examples of Formula I or Ia compounds are set forth above on pages 38-41.

Examples of Formula VI compounds are:

- 5 (i) N-(1-carboxy-3-phenylpropyl)-L-alanyl-L-proline;
- (ii) N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline;
- (iii) N-(1-ethoxycarbonyl-4-methylpentyl)-L-alanyl-L-proline;
- 10 (iv) N-(1-carboxy-5-aminopentyl)-L-alanyl-L-proline;
- (v) N- α -(1-carboxy-3-phenylpropyl)-L-lysyl-L-proline;
- (vi) N- α -(1-ethoxycarbonyl-3-phenylpropyl)-L-lysyl-L-proline;
- 15 (vii) N- α -[1-carboxy-3-(3-indolyl)-propyl]-L-lysyl-L-proline;
- (viii) N- α -[1-carboxy-3-(4-chlorophenyl)-propyl]-L-lysyl-L-proline;
- 20 (ix) N- α -[1-carboxy-2-phenylthioethyl]-L-lysyl-L-proline;
- (x) N- α -[1-carboxy-3-(4-chlorophenyl)-propyl]-L-lysyl-trans-4-methoxy-L-proline;
- (xi) N- α -[1-carboxy-5-aminopentyl]-L-lysyl-L-proline;
- 25 (xii) N- α -(1-carboxy-3-phenylpropyl)-L-ornithyl-L-proline;
- (xiii) ethyl N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-prolinate hydrochloride;
- 30 (xiv) N-[1-(ethoxycarbonyl)-3-(4-imidazolyl)propyl]-L-alanyl-L-proline.

2893P/1046A

2894P/1039A

- 70 -

17102IA

- (xv) N-[1-carboxy-3-(4-imidazolyl)propyl]-L-lysyl-L-proline;
- (xvi) N-(1(S)-carboxy-3-phenylpropyl)-L-alanyl-L-proline;
- 5 (xvii) N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline maleate salt;
- (xviii) N- α -(1(S)-carboxy-3-phenylpropyl)-L-lysyl-L-proline;
- (xix) ethyl N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-prolinate hydrochloride;
- 10 (xx) N- α -(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-lysyl-L-proline.

The above-described Formula VI compounds, their use and the method of preparation thereof are disclosed in U.S. Patent 4,374,829 the disclosure of which is hereby incorporated herein by reference.

The resolution of certain Formula I and Ia compounds into their optically pure enantiomers is as disclosed in U.S. Patents 4,424,355 and 4,435,579 which have been incorporated herein by reference.

The combination composition of the invention can contain varying amounts of the Formula I or Ia (i) antithrombotic compound and Formula VI (ii) antihypertensive compounds. The weight ratio of (i):(ii) can range from about 25 to 1; preferably from about 10 to 1. In addition to the active ingredients of (i) alone or of (i) and (ii) in combination, the compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, as necessary or desired. Such ingredients are generally referred to as carriers or diluents. Conventional procedures for

2893P/1046A

2894P/1039A

- 71 -

17102IA

preparing such compositions in appropriate dosage forms can be utilized. Whatever the dosage form, it will contain a pharmaceutically effective amount of the present composition.

5 The combination compositions can be administered orally or other than orally; e.g., parenterally, by insufflation, topically, rectally, etc.; using appropriate dosage forms; e.g., tablets, capsules, suspensions, solutions, and the like, for
10 oral administration; suspension emulsions, and the like, for parenteral administration; solutions for intravenous administration; and ointments, transdermal patches, and the like, for topical administration. These compositions are formulated similarly to the
15 compositions discussed on pages 46 to 51, above.

Treatment dosage for human beings for cardiovascular use can be varied as necessary. Generally, daily dosages of the composition of the invention can range from about 6000 to about 10 mg;
20 preferably, from about 3000 to about 20 mg.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form for cardiovascular use will vary depending upon the host treated and the particular
25 mode of administration. For example, a formulation intended for oral administration may contain from 5 mg to 5 gm of active agents compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of
30 the total composition. Dosage unit forms will generally contain between from about 20 mg to about 500 mg of active ingredients.

2893P/1046A

2894P/1039A

- 72 -

171021A

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The composition of this invention inhibits platelet accumulation at the damaged endothelial surface via the Formula I or Ia compound. This inhibitory effect is potentiated by the presence of the antihypertensive compound.

Thus, the compositions of the invention are useful in treating thrombosis and are also of value in the management of acute and chronic congestive heart failure.

In vivo testing of the composition of this invention in test animals (rabbits) can be used to demonstrate that this composition is pharmaceutically effective in decreasing platelet-related arterial thrombic formation.

To demonstrate the potentiation of the antihypertensive compound on the anti-thrombotic Formula I or Ia compound comprising the combination composition of the invention, the effect of these compounds on test animals (rabbits) can be determined separately and then in combination. The effect of a different class of antihypertensive agents singly and in combination with the Formula I or Ia compound of the invention can also be determined for comparative purposes. The methods employed are described in a

2893P/1046A

2894P/1039A

- 73 -

171021A

copending application, attorney docket no 17062, U.S. Serial No. 617,293, filed June 4, 1984, which is hereby incorporated herein by reference.

5 The following examples illustrate the preparation of the compounds of the present invention without, however, limiting the same thereto.

 All temperatures are in degrees Celsius.

10

EXAMPLE 1

A. Preparation of Hydrazine Starting Materials
1-[(4-Chlorophenyl)methyl]-1-(4-methylphenyl)
hydrazine

 A mixture of 10 g of p-tolylhydrazine
15 hydrochloride, 75 ml of toluene and 11.5 ml of triethylamine was heated at reflux for 60 minutes. Then, 7.1 g of p-chlorobenzyl chloride was added. After stirring 16 hours at reflux, triethylamine hydrochloride was filtered off and washed with ethyl
20 ether. The filtrate and washing were concentrated in vacuo and chromatographed on a silica gel column (hexane-ethylacetate, 9:1) to give 6.64 g of the title compound, (Compound No. 5 in Table 3).

25 B. Other hydrazines, similarly prepared, are also shown in Table 3.

30

2893P/1046A
2894P/1039A

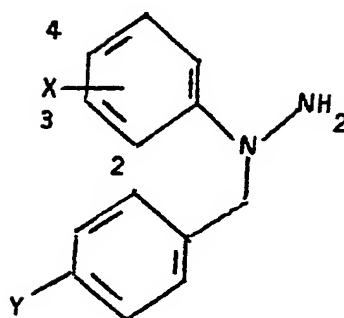
0166591

- 74 -

171021A

TABLE 3

Hydrazines



Compound No.	X	Y	Compound Name
1.	4-F	Cl	1-[(4-chlorophenyl)-methyl]-1-(4-fluorophenyl)hydrazine hydrochloride
2.	3,5-Cl ₂	Cl	1-[(4-chlorophenyl)-methyl]-1-(3,5-dichlorophenyl)hydrazine hydrochloride
3.	3-OMe	Cl	1-[(4-chlorophenyl)-methyl]-1-(3-methoxyphenyl)hydrazine hydrochloride
4.	3-Me	Cl	1-[(4-chlorophenyl)-methyl]-1-(3-methylphenyl)hydrazine hydrochloride

0166591

2893P/1046A

2894P/1039A

- 75 -

171021A

	5.	4-Me	Cl	1-[(4-chlorophenyl)-methyl]-1-(4-methylphenyl)hydrazine hydrochloride
5				
	6.	4-Cl	Cl	1-[(4-chlorophenyl)-methyl]-1-(4-chlorophenyl) hydrazine hydrochloride
10				
	7.	H	Cl	1-[(4-chlorophenyl)-methyl]-1-(phenyl) hydrazine hydrochloride
15				
	8.	4-Br	Cl	1-[(4-chlorophenyl)-methyl]-1-(4-bromophenyl)hydrazine hydrochloride
20				
	9.	4-OMe	SMe	1-[(4-methylthiophenyl)-methyl]-1-(4-methoxyphenyl) hydrazine hydrochloride
25				
	10.	4-OMe	Cl	1-[(4-chlorophenyl)-methyl]-1-(4-methoxyphenyl) hydrazine hydrochloride
30				
	11.	4-OMe	NO ₂	1-[(4-nitrophenyl)-methyl]-1-(4-methoxyphenyl)hydrazine hydrochloride

0166591

2893P/1046A

2894P/1039A

- 76 -

171021A

12. 4-F SMe 1-[(4-methylthiophenyl)-
methyl]-1-(4-fluoro-
phenyl) hydrazine hydro-
chloride

5

EXAMPLE 2


3 (or Beta)-[1-(p-Chlorobenzyl)-5-chloro-3-methyl-2-
indolyl]-propionic acid

10 Step 1:

To 1.84 g of 1,1-[(4-chlorophenyl)methyl]-1-(4-chlorophenyl) hydrazide hydrochloride in 60 cc of tert-butanol was added 868 mg of methyl 4-oxo-hexanoate. The reaction mixture was refluxed under
15 nitrogen for 16 hours. The resulting reaction mixture was then evaporated to dryness and the resulting residue suspended in CH_2Cl_2 . The solid material was then filtered. The filtrate was washed with water, dried and evaporated. The resulting
20 syrup was then chromatographed on silica gel to give 1.47 g of indole derivative (65%).

NMR: H^1 NMR (CDCl_3): 2.25 ppm (Me, 3H, singlet); 2.43 (CH_2 , 2H, triplet); 3.01 (CH_2 , 2H, triplet); 3.64

25

(OMe, 3H, singlet); 5.29 (CH_2 -, 2H, singlet); 6.83

(H-2' and H-6', 2H, d); 7.1 (H-6, and H-7, 2H, multiplet); 7.25 (H-3' and H-5', 2H); 7.49 (H-4, 1H, singlet).
30

2893P/1046A

2894P/1039A

- 77 -

171021A

Step 2:

To 1.06 g of methyl ester in 350 ml of EtOH was added 169 mg of sodium hydroxide dissolved in 3 ml of H₂O. The resulting solution was stirred at room temperature for 16 hours. The reaction mixture was then acidified with HCl (1N) and concentrated. The resulting solution was then extracted with CH₂Cl₂ (3 times). The combined organic layer was washed with brine, dried over MgSO₄, and evaporated to give 1 g of solid material (100% yield). An analytical sample of this material was prepared by triturating the resulting solid material with hexane followed by a filtration (800 mg).

Analysis calculated for C₁₉H₁₇Cl₂NO₂:
C, 62.99; H, 4.74; N, 19.58
Found: C, 63.19; H, 4.78; N, 19.35.

EXAMPLE 3

3 (or Beta)-[1-(p-Chlorobenzyl)-3-methyl-5-fluoro-2-indolyl]-propionic acid

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-fluorophenyl)-hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials and ethanol as the solvent, the title compound was prepared.

Analysis calculated for C₁₉H₁₇ClFNO₂:
C, 65.98; H, 4.95; Cl, 10.25
Found: C, 65.56; H, 5.17; Cl, 10.52.

2893P/1046A

2894P/1039A

- 78 -

171021A

EXAMPLE 4

3 (or Beta)-[1-(p-Chlorobenzyl)-3-methyl-4,6-dichloro-
2-indolyl]propionic acid

Following the procedure of Example 2, but
5 using 1-[(4-chlorophenyl)methyl]-1-(3,5-dichloro-
phenyl)hydrazine hydrochloride and methyl
4-oxohexanoate as the starting materials and ethanol
as the solvent, the title compound was prepared.

Analysis calculated for $C_{19}H_{16}O_2Cl_3N$:

10 C, 57.52; H, 4.06

Found: C, 57.40; H, 4.20.

EXAMPLE 5

3 (or Beta)-[1-(p-Chlorobenzyl)-3-methyl-4-methoxy-2-
15 indolyl]propionic acid

Following the procedure of Example 2, but
using 1-[(4-chlorophenyl)methyl]-1-(3-methoxyphenyl)-
hydrazine hydrochloride and ethyl 4-oxohexanoate as
the starting materials and ethanol as the solvent,
20 the title compound was prepared.

Analysis calculated for $C_{20}H_{20}O_3NCl$:

C, 67.12; H, 5.63

Found: C, 67.40; H, 5.43.

25

EXAMPLE 6

3 (or Beta)-[1-(p-chlorobenzyl)-3-methyl-6-methoxy-2-
indolyl]propionic acid

Following the procedure of Example 2, but
using 1-[(4-chlorophenyl)methyl]-1-(5-methoxyphenyl)-
30 hydrazine hydrochloride and methyl 4-oxohexanoate as
the starting materials and tert-butanol as the
solvent, the title compound was prepared.

2893P/1046A

2894P/1039A

- 79 -

171021A

Analysis calculated for $C_{20}H_{20}O_3NCl$:

C, 67.12; H, 5.63; N, 3.91; Cl, 9.90

Found: C, 67.08; H, 5.64; N, 4.09.

5

EXAMPLE 7

3 (or Beta)-[1-(p-Chlorobenzyl)-3,4-dimethyl-2-indolylpropionic acid and 3 (or Beta)-[1-(p-chlorobenzyl)-3,6-dimethyl-2-indolyl]propionic acid (as a mixture)

10

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(3-methylphenyl)-hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials and t-butanol as the solvent, the title compounds were prepared.

15

Analysis calculated for $C_{20}H_{20}NClO_2$:

C, 70.26; H, 5.89; N, 4.09; Cl, 10.37

Found: C, 70.52; H, 5.57; N, 4.56; Cl, 10.03.

EXAMPLE 8

20

1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-(4'-carboxy-butyl)indole

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-methoxyphenyl)-hydrazine hydrochloride and methyl 6-oxooctanoate as the starting materials and methanol as the solvent, the title compound was prepared.

25

Analysis calculated for $C_{22}H_{24}NO_3Cl$:

C, 68.57; H, 6.23; N, 3.63

Found: C, 68.45; H, 6.41; N, 3.35.

30

2893P/1046A

2894P/1039A

- 80 -

171021A

EXAMPLE 9

3 (or Beta)-[1-(p-Chlorobenzyl)-3,5-dimethyl-2-indolyl]propionic acid

5 Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-methylphenyl)-hydrazine hydrochloride and methyl 4-oxohexanoate as the reactants and ethanol as the solvent, the title compound was prepared.

Analysis calculated for $C_{20}H_{20}O_2NCl$:

10 C, 70.31; H, 5.90; N, 4.1; Cl, 10.37

Found: C, 70.37; H, 5.85; N, 4.10; Cl, 10.15.

EXAMPLE 10

15 1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-(3-carboxypropyl)indole

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-methoxyphenyl)-hydrazine hydrochloride and methyl 5-oxoheptanoate as the starting materials and ethanol as the solvent, the title compound was prepared.

20 Analysis calculated for $C_{21}H_{22}NO_3Cl$:

C, 67.83; H, 5.92; N, 3.76

Found: C, 67.92; H, 5.97; N, 3.84.

EXAMPLE 11

25 3 (or Beta)-[1-(p-Chlorobenzyl)-3-methyl-2-indolyl]-propionic acid

30 Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(phenyl)hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials and tert-butanol as the solvent, the title compound was prepared.

2893P/1046A

2894P/1039A

- 81 -

171021A

Analysis calculated for $C_{19}H_{18}O_2ClN$:

C, 67.15; H, 5.33; N, 4.12; Cl, 10.43

Found: C, 67.77; H, 5.42; N, 4.48; Cl, 10.48.

5

EXAMPLE 12

3 (or Beta)-[1-(p-Chlorobenzyl)-5-bromo-3-methyl-2-indolyl]propionic acid

Following the procedure of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-bromophenyl)-hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials and t-butanol as the solvent, the title compound was prepared.

Analysis calculated for $C_{19}H_{17}ClO_2BrN$:

C, 56.10; H, 4.21;

Found: C, 56.07; H, 4.27.

EXAMPLE 13

1-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(2-carboxyethyl)indole

Following the procedure of Example 2, but using 1-[(4-methylthiophenyl)methyl]-1-(4-methoxyphenyl)hydrazine hydrochloride and methyl 4-oxohexanoate as the starting materials and tert-butanol as the solvent, the title compound was prepared.

Analysis calculated for $C_{21}H_{23}NO_3S$:

C, 68.29; H, 6.23; N, 3.79

Found: C, 68.03 H, 6.12; N, 3.76.

30

2893P/1046A

2894P/1039A

- 82 -

171021A

EXAMPLE 141-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(2-carboxyethyl)indole S-oxide

Using the methyl ester of the title compound
5 of Example 13 as the starting material, 250 mg were
dissolved in 20 ml of dichloro methane and cooled to
0°C. Metachloroperoxybenzoic acid, 138 mg, was added
and the reaction stirred at 0°C for 1 hour. 200 mg
anhydrous Ca(OH)_2 was added and the reaction
10 filtered and evaporated to dryness. The methyl ester
so obtained was hydrolyzed according to the
conditions described in Example 2.

Analysis calculated for $\text{C}_{21}\text{H}_{23}\text{NO}_4\text{S}$:

C, 63.45; H, 5.70; N, 3.47

15 Found: C, 63.55; H, 5.67; N, 3.32.

EXAMPLE 151-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(3-carboxypropyl)indole

20 Following the method of Example 2, but using
1-[(4-methylthiophenyl)methyl]-1-(4-methoxyphenyl)-
hydrazine hydrochloride and methyl 4-oxoheptanoate as
the starting materials and tert-butanol as the
solvent, the title compound was prepared.

25 Analysis calculated for $\text{C}_{22}\text{H}_{25}\text{NO}_3\text{S} \cdot 1/2 \text{H}_2\text{O}$:

C, 67.86; H, 6.64; N, 3.50

Found: C, 66.85; H, 6.63; N, 3.31

2893P/1046A

2894P/1039A

- 83 -

171021A

EXAMPLE 16

4-[1-(p-Chlorobenzyl)-3-methyl-5-fluoro-2-indolyl]-
butanoic acid

5 Following the method of Example 2, but using
1-[(4-chlorophenyl)methyl]-1-(4-fluorophenyl)hydrazine
hydrochloride and methyl 5-oxoheptanoate as the
starting materials and tert-butanol as the solvent,
the title compound was prepared.

Analysis calculated for $C_{20}H_{19}ClFNO_2$:

10 C, 66.76; H, 5.32; Cl, 9.85

Found: C, 66.89; H, 5.24; Cl, 10.26.

EXAMPLE 17

3 (or Beta)-[1-(p-Thiomethylbenzyl)-3-methyl-5-fluoro-
15 2-indolyl]propanoic acid

 Following the procedure of Example 2, but
using 1-[(4-methylthiophenyl)methyl]-1-(4-fluoro-
phenyl)hydrazine hydrochloride and methyl 4-oxo-
hexanoate as the starting materials and tert-butanol
20 as the solvent, the title compound was prepared.

Analysis calculated for $C_{20}H_{20}O_2FSN$:

 C, 67.20; H, 5.64; N, 3.91

Found: C, 67.21; H, 5.91; N, 3.88.

EXAMPLE 18

25

3 (or Beta)-[1-p-Methylsulfoxylbenzyl)-3-methyl-5-
fluoro-2-indolyl]-propanoic acid

 Using the title compound of Example 17,
treated according to the procedure described in
30 Example 14, the title compound was obtained.

Analysis calculated for $C_{20}H_{20}FNO_3S$:

 C, 64.32; H, 5.39; N, 3.75

Found: C, 64.18; H, 5.65; N, 3.48.

2893P/1046A

2894P/1039A

- 84 -

171021A

EXAMPLE 19

3-[1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-indolyl]-
butanoic acid

5 Following the method of Example 2, but using
1-[(4-chlorophenyl)methyl]-1-(4-methoxyphenyl)-
hydrazine hydrochloride and methyl 3-methyl-4-
oxohexanoate as the starting materials and methanol
as the solvent, the title compound was prepared.

Analysis calculated for $C_{21}H_{22}NO_3Cl \cdot H_2O$:

10 C, 64.78; H, 6.13; N, 3.59

Found: C, 65.86; H, 6.12; N, 3.37.

EXAMPLE 20

15 3-Methyl-4-[1-p-chlorobenzyl-5-methoxy-3-methylindol-
2-yl]butanoic acid

20 Following the method of Example 2, but using
1-[(4-chlorophenyl)methyl]-1-(4-methoxyphenyl)hydrazine
hydrochloride and 3-methyl-5-oxoheptanoic acid as
the starting materials and isopropanol as the
solvent, the title compound was prepared.

Analysis calculated for $C_{22}H_{24}O_3NCl$:

C, 68.48; H, 6.27; N, 3.63; Cl, 9.19

Found: C, 68.49; H, 6.50; N, 3.55; Cl, 8.93.

25

EXAMPLE 21

3-Methyl-4-[1-p-chlorobenzyl-5-fluoro-3-methylindol-2-
yl]butanoic acid

30 Following the method of Example 2, but using
1-[(4-chlorophenyl)methyl]-1-(4-fluorophenyl)hydrazine
hydrochloride and 3-methyl-4-oxoheptanoic acid as the
starting materials and isopropanol as the solvent,
the title compound was prepared.

2893P/1046A

2894P/1039A

- 85 -

171021A

Analysis calculated for $C_{21}H_{21}O_2NClF$:

Calc.: C, 67.47; H, 5.66; N, 3.75; Cl, 9.48; F, 5.08

Found: C, 67.57; H, 5.90; N, 3.60; Cl, 9.44; F, 4.50

5

EXAMPLE 22

3-(1-p-Chlorobenzyl-3-methyl-5-methoxyindol-2-yl)-2,2-dimethylpropanoic acid

Following the method of Example 2, but using 1-[(4-chlorophenyl)methyl]-1-(4-methoxyphenyl)hydrazine hydrochloride and methyl 2,2-dimethyl-4-oxohexanoate as the starting materials and tert-butanol as the solvent, the title compound was prepared.

Analysis calculated for $C_{22}H_{24}NO_3Cl$:

Calc.: C, 64.48; H, 6.40; N, 3.63

15 Found: C, 68.32; H, 6.37; N, 3.53.

EXAMPLE 23

3-[1-p-Chlorobenzyl-5-hydroxy-3-methylindol-2-yl]-propionic acid

20 Beginning with 3-[1-p-chlorobenzyl-5-methoxy-3-methylindol-2-yl]propionic acid which is described in J. Med. Chem., 1252 (1968), (2.7 g) was dissolved in 20 ml CH_2Cl_2 at 0°C. 7.6 ml BBr_3 (1M in CH_2Cl_2) was added dropwise and the reaction stirred for 60 minutes. After 180 minutes at 23°C, 25 another 4 ml BBr_3 solution was added. The reaction was stirred for a further 180 minutes. The reaction was cooled to -20°C and 15 ml MeOH added. The organic phase was washed with $NaHCO_3$ (aqueous), 30 dried with Na_2SO_4 and chromatographed on silica gel. Hydrolysis of the methyl ester was carried out as described in Example 2 to yield 2.2 g of the title compound.

2893P/1046A

2894P/1039A

- 86 -

171021A

Analysis calculated for $C_{19}H_{18}O_3ClN$:

C, 66.37; H, 5.27; N, 4.07; Cl, 10.31

Found: C, 66.54; H, 5.16; N, 3.85; Cl, 10.65.

5

EXAMPLE 24

3-[1-p-Chlorobenzyl-5-acetoxy-3-methylindol-2-yl]-
propionic acid

Using the title compound of Example 23 as
starting material, (1 g) was dissolved in CH_2Cl_2
10 (20 ml) at 0°C and 1 ml pyridine added. 1.8 g acetic
anhydride was added and the reaction let stir at 23°
for 16 hours. The organic phase was washed with
 H_2O (5 X 5 ml), evaporated and chromatographed.

Analysis calculated for $C_{21}H_{20}O_3NCl$:

15 Calc.: C, 65.37; H, 5.22; N, 3.63; Cl, 9.19

Found: C, 65.35; H, 5.09; N, 3.54; Cl, 9.25.

EXAMPLE 25

3-[4,6-dichloro-1-(4-chlorobenzyl)-3-methyl-1H-indol-2-
20 yl] propanoic acid

Following the method of Example 2, but using
1-[1-(chlorophenyl)methyl-1-(3,5-dichlorophenyl)
hydrazine hydrochloride and methyl 4-oxohexanoate as
the starting materials, in t-butanol as solvent, the
25 title compound was prepared.

Analysis calculated for $C_{19}H_{16}NCl_3O_2$

C	H	
57.52	4.06	Calc.
57.40	4.20	Found

30

2893P/1046A

2894P/1039A

- 87 -

17102IA

EXAMPLE 26

3-[1-(4-chlorobenzyl)-4-methoxy-3-methyl-1H-indol-2-yl] propanoic acid

Following the method of Example 2, but using
5 1-[4-(chlorobenzyl)-1-(3-methoxy phenyl) hydrazine
hydrochloride and methyl-4-oxohexanoate as the
starting materials in t-butanol as solvent, the title
compound was prepared, m.p. 145°C.

Analysis calculated for $C_{20}H_{20}O_3NCl$:

10 Calc.: C, 67.12; H, 5.63

Found: C, 67.40; H, 5.43.

EXAMPLE 27

15 1-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-
methoxy acetic acid

Step 1. Methyl 1-(4-chlorobenzyl)-5-fluoro-3-methyl-
indol-2-carboxylate

Following the procedure of Example 42 Step
1, but using 1-(4-chlorobenzyl)-1-(4-fluorophenyl)-
20 hydrazine in place of 1-(4-chlorobenzyl)-1-(4-
methoxyphenyl)hydrazine, there was obtained the title
compound of Step 1.

Step 2. 1-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-
25 2-yl]methanol

1.50 g 1-(4-chlorobenzyl)-3-methyl-5-fluoro-
1H-indole-2-carboxylate Me ester was dissolved in 50
ml dry THF. Diisobutyl aluminum hydride (1.5 M) in
tetrahydrofuran (THF) (2 equivalents) was added at
30 -78°C. The reaction was stirred for 16 hrs., allowed
to reach room temperature and quenched with NH_4Cl
(aq.). The organic phase was separated, dried

0166591

2893P/1046A

2894P/1039A

- 88 -

171021A

(Na_2SO_4) and evaporated to produce 1.32 g of product which was purified on column chromatography to yield the title compound of Step 2.

- 5 Step 3. The title compound from Step 2 (1.0 g) was dissolved in dry dimethylformamide (DMF) (10 ml) at -20°C . Potassium hexamethyl disilazane base in toluene (0.69 M) was added (1.1 molar equivalents) and the reaction stored for 1 hr. Ethyl 2-bromo
10 acetate (580 mg) (1.2 equivalents) was added and the reaction stirred for 16 h at 21°C . Water was added (3 ml). The product was isolated after extraction from the aqueous DMF with ether. Following purification on column chromatography, the title ethyl ester was
15 hydrolysed in 3N NaOH according to the procedure in Example 2.

M.P. = 154°

EXAMPLE 28

- 20 3-[1-(4-bromobenzyl)-3-methyl-5-methoxyindol-2-yl]-
2,2-dimethylpropanoic acid

- Following the method of Example 2, but using 1-[4-bromobenzyl]-1-(4-methoxy phenyl) hydrazine hydrochloride and methyl-2,2-dimethyl-4-oxohexanoate
25 as the starting materials, using t-butanol as the solvent, the title compound was prepared.

M.P. = 170°

2893P/1046A

2894P/1039A

- 89 -

171021A

EXAMPLE 29

3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]
2-methyl propanoic acid

Following the method of Example 2, but using
5 1-[4-chlorobenzyl]-1-(4-chlorophenyl) hydrazine
hydrochloride and methyl-3-methyl-4-oxohexanoate as
starting materials, using t-butanol as solvent, the
title compound was prepared.

M.P. = 128°

10

EXAMPLE 30

3-[1-(4-iodobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-
dimethyl propanoic acid

Following the method of Example 2, but using
15 1-[4-iodobenzyl]-1-(4-methoxyphenyl)hydrazine
hydrochloride and methyl-2,2-dimethyl-4-oxo-hexanoate
as starting materials, using t-butanol as solvent,
the title compound was prepared.

M.P. = 152°

20

EXAMPLE 31

3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-
2,2-dimethyl propanol

700 mg of 3-[1-(4-chlorobenzyl)-3-methyl-
25 5-methoxyindol-2-yl]-2,2-dimethyl propanoic acid
methyl ester was dissolved in 20 ml dry tetrahydro-
furan. The reaction was cooled to -78°C and 2
equivalents di-isobutyl aluminium hydride (DIBAL) in
THF was added. The reaction was allowed to warm to
30 room temperature and quenched with NH₄Cl (aq.).
Ethyl acetate was added (75 ml) and the organic phase

2893P/1046A

2894P/1039A

- 90 -

171021A

separated, dried and evaporated. The product was isolated by column chromatography.

M.P. = 100.1°

5

EXAMPLE 32

3-[1-(4-chlorobenzyl)-3-methoxy-5-hydroxyindol-2-yl]-
2,2-dimethyl propanoic acid

Following the method of Example 23, but using the product of Example 22 as starting material, the
10 title compound was prepared.

M.P. = 137°

EXAMPLE 33

3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-
15 propanol

Following the method of Example 31, but using the starting material of Example 23, the title compound was prepared.

M.P. = 118°

20

EXAMPLE 34

3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-
2,2-dimethyl propanoic acid

Following the method of Example 2, but using
25 1-[4-chlorobenzyl]-1-(4-fluorophenyl)hydrazine hydrochloride 1.9 g and 2,2-dimethyl-4-oxohexanoic acid (950 mg) as starting materials, in t-butanol as solvent, after 16 hrs. at reflux, the solvent was removed in vacuo, and the title compound was isolated
30 by crystallization and filtration, followed by crystallization from hot ethyl acetate:hexane 9:1.

0166591

2893P/1046A

2894P/1039A

- 91 -

171021A

Analysis for $C_{21}H_{21}NO_2ClF$

C	H	
67.47	5.62	Calc.
67.53	5.70	Found

5 M.P. = 124°

EXAMPLE 35

3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-3-methyl propanoic acid

10 Following the method of Example 2, but using 1-[4-chlorobenzyl]-1-(4-fluorophenyl) hydrazine hydrochloride and methyl 3-methyl-4-oxohexanoate as starting materials, the title compound was prepared.

M.P. = 143°

15

EXAMPLE 36

3-[1-(4-chlorobenzyl)-3-methyl-5-hydroxyindol-2-yl] butanoic acid

20 Following the method of Example 23, but using the product of Example 19 as starting material, the title compound was prepared.

M.P. = 162°

EXAMPLE 37

25 Methyl 4-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-butanoate

Following the method of Example 44, but using the product of Example 16 as starting materials, the title compound was prepared.

30 Analysis for $C_{21}H_{21}NO_2FCl$

C	H	
67.47	5.62	Calc.
67.53	5.70	Found

2893P/1046A

2894P/1039A

- 92 -

17102IA

EXAMPLE 383-[1-(4-chlorobenzyl)-3-methyl-4-propyl-5-hydroxyindol-2-yl]-propanoic acid

210 mg of the methyl ester of Example 39 was heated in a Kugelrohr vacuum distillation apparatus at 200°C without vacuum for 90 min. The product was then distilled in vacuo at 0.1 mm Hg, 200°C. The liquid obtained was chromatographed on a preparative plate (hexane 8, ethyl acetate 2). 125 mg. of 3-[1-(4-chlorobenzyl)-3-methyl-4-(3-propyl)-5-hydroxyindol-2-yl]propanoic acid methyl ester was isolated, which was then hydrogenated with 10% palladium on charcoal in 10 ml of MeOH with 40 psi H₂ for 3 min. The methyl ester title compound was isolated from a preparative plate (SiO₂) (hexane 8, ethyl acetate 2) (82 mg) and the corresponding acid was obtained from hydrolysis as shown in Example 2.

Analysis calculated for C₂₂H₂₄O₃NCl + 2H₂O

	C	H	
62.43		6.06	Calc.
62.62		5.73	Found

EXAMPLE 393-[1-(4-chlorobenzyl)-3-methyl-5-prop-2-enoxyindol-2-yl]-propanoic acid

Using 845 mg of the product of Example 23 as starting material, diluted in 23 ml of dimethyl ketone, 476 mg of potassium carbonate and 225 µl of allyl bromine was added. The reaction was refluxed overnight. The reaction was then diluted with water and the acetone removed in vacuo. Then the reaction

2893P/1046A

2894P/1039A

- 93 -

17102IA

was extracted with $\text{CH}_3\text{CO}_2\text{Et}$ and the organic phase was dried and concentrated to yield after flash chromatography (hexane 8, ethyl acetate 2) 790 mg of the compound, which was then hydrolyzed following the procedure of Example 2.

Analysis calculated for $\text{C}_{22}\text{H}_{22}\text{O}_3\text{NCl}$

C	H	
68.83	5.77	Calc.
68.88	5.89	Found

M.P. = 131.2°

EXAMPLE 40

Methyl-3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-dimethyl-propanoate

Following the method of Example 45, but using the product of Example 22 as starting material, the title compound was prepared.

M.P. = 110°

EXAMPLE 41

3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2-methyl-butanoic acid

Step 1. Ethyl 2,3-dimethyl-4-oxo-hexanoate

To 4.23 g ethyl 2-bromopropionate in 50 ml acetonitrile was added 2.5 g N-[3-(pent-2-enyl)]-pyrrolidine. The reaction was refluxed for 16 hr. The solvent was removed in vacuo and the product was isolated by chromatography on silica gel to yield 1.5 g of the title compound which was used as such in the second step.

2893P/1046A

2894P/1039A

- 94 -

171021A

Step 2. Following the method of Example 2, but using 1-[4-chlorobenzyl]-1-(4-fluorophenyl)hydrazine hydrochloride and ethyl 2,3-dimethyl-4-oxo-hexanoate as starting materials, the title compound
5 was prepared.

M.P. = 177°

EXAMPLE 42

1-(4-chlorobenzyl)-3-methyl-5-methoxy-1H-indole-2-
10 methoxy acetic acid.

Step 1. Methyl 1-(4-chlorobenzyl)-5-methoxy-3-methyl-
indol-2-carboxylate

To a solution of 1 g 2-keto butyric acid in 35 ml MeOH (to which had previously been added 1 ml
15 CH_3COCl at 0°C) was added 12.82 g N-benzyl-4-methoxyphenyl hydrazine hydrochloride. The solution was refluxed for 1 hr., the methanol distilled off and a crystalline pasty residue triturated with
20 methanol to give 2.6 g crystalline material. The crystals were swished with 9:1 hexane:EtOAc overnight to yield 2.0 g pure product, which was used as such in the next step.

Step 2. 1-(4-chlorobenzyl)-3-methyl-5-methoxy-1H-
25 indole-2-methanol.

1.50 g 1-(4-chlorobenzyl)-3-methyl-5-methoxy-1H-indole-2-carboxylate methyl ester was dissolved in 50 ml dry THF. Diisobutyl aluminum hydride (1.5 M) in THF (2 equivalents) was added at -78°C. The
30 reaction was stirred for 16 hrs., allowed to reach room temperature and quenched with NH_4Cl (aq.). The organic phase was separated, dried (Na_2SO_4)

2893P/1046A

2894P/1039A

- 95 -

171021A

and evaporated to produce 1.32 g of product which was purified on column chromatography to yield the title compound of Step 2.

- 5 Step 3. The product from Step 2 above (1.0 g) was dissolved in dry DMF (10 ml) at -20°C. Potassium hexamethyl disilazane base in toluene (0.69 M) was added (1.1 molar equivalents) and the reaction stirred for 1 hr. Ethyl 2-bromo acetate (580 mg) = 1.2
10 equivalents was added and the reaction stirred for 16 h at 21°C. Water was added (3 ml). The product was isolated after extraction from the aqueous DMF with ether. Following purification on column chromatography, the title ethyl ester was hydrolysed in 3N
15 NaOH according to the procedure in Example 2.

M.P. = 128°

EXAMPLE 43

- 20 3-[1-(4-chlorobenzyl)-3-methyl-5-chloroindol-2-yl]-2,2-dimethyl-propanoic acid

- Following the method of Example 2, but using 1-[4-chlorobenzyl]-1-[4-chlorophenyl]hydrazine hydrochloride and methyl-2,2-dimethyl-4-oxohexanoate in t-butanol as solvent, the title compound was
25 prepared.

M.P. = 142.5°

EXAMPLE 44

- 30 Methyl-3-[-1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl] propanoate

3-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl] propanoic acid (50 g) was dissolved in

0166591

2893P/1046A

2894P/1039A

- 96 -

171021A

400 ml absolute methanol and cooled to 0°C. Boron trifluoride etherate (50 ml) was added slowly over 25 min. The reaction was quenched after 16 hr. by the addition of water/ NaHCO_3 . Upon evaporation, the water was removed by extraction with CH_2Cl_2 . The organic phase was dried and concentrated to yield 47 g of the title methyl ester.

Analysis calculated for $\text{C}_{20}\text{H}_{21}\text{NO}_3\text{Cl}$:

	C	H	N	Cl
10 Calc.:	67.83	5.96	3.77	9.53
Found:	67.67	5.21	3.68	9.68

EXAMPLE 45

3-[1-(4-aminobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid

Step 1. 3-[1-(4-nitrobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid

Following the method of Example 2, but using 1-[(4-nitrophenyl)methyl-1-(4-methoxyphenyl) hydrazine hydrochloride and methyl 2,2-dimethyl-4-oxo-hexanoate as the starting materials and tert-butanol as the solvent, the title compound was prepared.

Analysis calculated for $\text{C}_{22}\text{H}_{24}\text{O}_5$

	C	H	N
25 Calc.:	66.67	6.06	7.07
Found:	67.00	6.12	7.10

Step 2. 500 mg of the product of Step 1 was dissolved in 35 ml of absolute ethanol and 50 mg of 10% palladium on carbon catalyst added. The suspension was hydrogenated at 50 psi until consumption of 2 mole equivalents of hydrogen occurred. The

0166591

2893P/1046A

2894P/1039A

- 97 -

171021A

catalyst was removed by filtration and the title compound was isolated by vacuum distillation of the solvent (489 mg).

M.P. = 173°

5

EXAMPLE 46

4-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl butanoic acid

Following the method of Example 2, but using 1-[(4-chlorobenzyl)-1-(4-methoxyphenyl)] hydrazine hydrochloride and methyl 2,2-dimethyl-5-oxoheptanoate as starting materials, the title compound was prepared.

Analysis calculated for $C_{23}H_{25}NO_3Cl$

	C	H	N
Calc.:	69.28	6.52	3.51
Found:	69.21	6.93	3.22

EXAMPLE 47

4-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-1H-indol-2-yl]-2,2-dimethyl butanoic acid

Following the method of Example 2, but using 1-[4-chlorobenzyl]-1-[4-fluorophenyl] hydrazine hydrochloride and methyl-2,2-dimethyl-5-oxoheptanoate as starting materials, in t-butanol as solvent, the title compound was prepared.

Analysis calculated for $C_{22}H_{23}NO_2ClF$

	C	H	N
Calc.:	68.13	5.60	3.61
Found:	68.34	5.69	3.41

0166591

2893P/1046A

2894P/1039A

- 98 -

171021A

EXAMPLE 48

4-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-3-methyl butanoic acid

5 Following the method of Example 23, but using 4-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-3-methyl butanoic acid as starting material, the title compound was prepared.

Analysis calculated for $C_{21}H_{22}NO_3Cl$

	C	H	N	
10	67.13	5.92	3.76	Calc.
	68.36	5.69	3.51	Found

EXAMPLE 49

15 4-[1-(4-methylthiobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-3-methyl butanoic acid

20 Following the method of Example 2, but using 1-[4-methylthiobenzyl]-1-[4-methoxyphenyl] hydrazine hydrochloride and methyl-3-methyl-5-oxoheptanoate as starting materials, in t-butanol as solvent, the title compound was prepared

Analysis calculated for $C_{21}H_{27}NO_3S$

	C	H	N	
	69.56	6.92	3.52	Calc.
25	69.85	7.20	3.50	Found

EXAMPLE 50

3-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid

30 Following the method of Example 23, but using 3-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid as starting material, the title compound was prepared.

M.P. = 110° (decomposition)

0166591

2893P/1046A

2894P/1039A

- 99 -

17102IA

EXAMPLE 51

3-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-3-methyl propanoic acid

5 Following the method of Example 23, but using 3-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-3-methyl propanoic acid as starting material, the title compound was prepared.

	$C_{20}H_{20}NO_3Cl$			
	C	H	N	
10	67.13	5.59	3.9	Calc.
	67.22	5.74	3.97	Found

EXAMPLE 52

15 3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid

The title compound of Example 50 was treated according to the method described in Example 39 using ethyl bromide as the alkylating agent. The product was isolated by chromatography on silica gel

20 (CH_2Cl_2) .
M.P. = 148°

25

30

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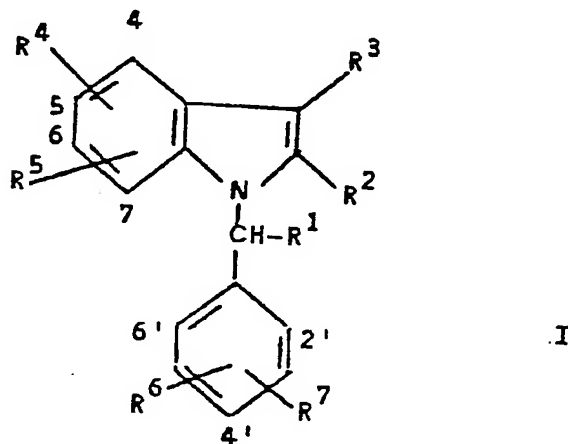
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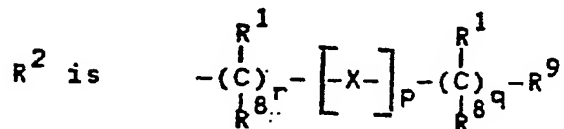
CLAIMS

1. A pharmaceutical composition useful as a prostaglandin antagonist in mammals comprising a prostaglandin antagonizing amount of compound of the Formula I or a compound that is a pharmaceutically acceptable salt thereof:



where

R^1 is H or alkyl of 1 to 6 carbons or R^1 and R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7;



where

each R^8 is independently H, OH, C_1 to C_4 -O-alkyl or alkyl of 1 to 4 carbons; or an R^1 and an R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7.

R^9 is COOR^1 ; CH_2OH ; CHO ; tetrazole;
 $\text{NHSO}_2\text{R}^{10}$ wherein R^{10} is OH , alkyl or alkoxy of
 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons,
 phenyl or phenyl substituted by alkyl or alkoxy
 5 groups of 1 to 3 carbons, halogen, hydroxy, COOH , CN ,
 formyl or acyl to 1 to 6 carbons; $\text{CONHSO}_2\text{R}^{10}$;
 hydroxymethylketone; CN ; or $\text{CON}(\text{R}^8)_2$;

X is O ; S ; SO ; SO_2 ; NR^{11} wherein R^{11}
 is H , alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons,
 10 CN ; CR^1R^8 ;

or the unit $\begin{array}{c} \text{R}^1 \quad \text{R}^8 \\ | \quad | \\ -\text{C} \equiv \text{C}- \end{array}$ wherein the dotted line
 represents an optional triple bond and in which the
 R^1 and R^8 substituents are absent when a triple
 15 bond is present;

r and q are each independently 0 to 5 and p
 is 0 or 1 provided that the total of p , q and r is 2
 to 6;

R^3 is H , alkyl of 1 to 6 carbons; phenyl
 20 or phenyl substituted by R^4 ; or C_1 to C_4 alkyl-
 phenyl or C_1 to C_4 alkylphenyl in which the
 phenyl is substituted by R^4 ;

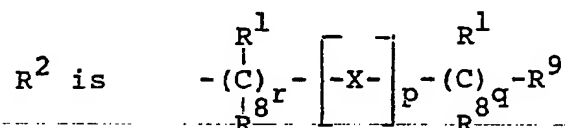
R^4 , R^5 , R^6 and R^7 are each
 independently selected from:

- 25 (1) hydrogen;
 (2) alkyl having 1 to 6 carbon atoms;
 (3) alkenyl having 2 to 6 carbon atoms;
 (4) $-(\text{CH}_2)_n\text{M}$
 wherein n is 0 to 3 and M is
 30 a) OR^{12} ;
 b) halogen;
 c) CF_3 ;

- 5
- d) SR^{12} ;
- e) phenyl or substituted phenyl
wherein substituted phenyl is
as defined below in the
definition of R^{12} ;
- f) COOR^{13} ;
- g) $\text{C}(=\text{O})\text{-R}^{14}$;
- h) tetrazole;
- 10
- i) $\text{-NH-C}(=\text{O})\text{-R}^{15}$ wherein R^{15} is
 C_1 to C_6 alkyl, benzyl or
phenyl;
- j) $\text{-NR}^{13}\text{R}^{13}$;
- 15
- k) $\text{-NHSO}_2\text{R}^{16}$ wherein R^{16}
is C_1 to C_6 alkyl,
phenyl, or CF_3 ;
- l) $\text{-C}(=\text{O})\text{-CH}_2\text{OH}$;
- 20
- m) -SOR^{12} ;
- n) $\text{-CONR}^{13}\text{R}^{13}$;
- o) $\text{-SO}_2\text{NR}^{13}\text{R}^{13}$;
- p) $\text{-SO}_2\text{R}^{12}$;
- 25
- q) NO_2 ;
- r) $\text{O-C}(=\text{O})\text{-R}^{14}$;
- s) $\text{O-C}(=\text{O})\text{-NR}^{13}\text{R}^{13}$;
- 30
- t) $\text{O-C}(=\text{O})\text{-OR}^{15}$;
- u) CN ;

each R^{12} independently is H; C_1 to C_6 alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are C_1 to C_3 alkyl, halogen, CN, CF_3 , $COOR^{13}$, CH_2COOR^{13} , C_1 to C_3 alkoxy, or C_1 to C_4 perfluoroalkyl;
 each R^{13} is independently H, phenyl or C_1 to C_6 alkyl; and,
 each R^{14} independently is H, $(CH_2)_nCOOR^{13}$ wherein n is 0 to 4, C_1 to C_6 alkyl, CF_3 , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of R^{12} ; and a pharmaceutically acceptable carrier.

2. A composition according to Claim 1, wherein:
 R^1 is H or alkyl of 1 to 3 carbons or R^1 and R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7, with the proviso that R^1 on the benzylic carbon attached to the indole nitrogen is H;



wherein:

each R^8 is independently H, or alkyl of 1 to 4 carbons; or an R^1 and an R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7.
 R^9 is $COOR^1$; CH_2OH ; CHO ; or tetrazole;
 X is O; S; SO; SO_2 ; NR^{11} wherein R^{11} is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN; CR^1R^8 ;

or the unit $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \equiv C- \end{array}$ wherein the dotted line represents an optional triple bond and in which the R^1 and R^8 substituents are absent when a triple bond is present;

r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p , q and r is 2 to 3;

R^3 is alkyl of 1 to 6 carbons, but is not cycloalkyl;

R^4 , R^5 , R^6 and R^7 are each independently selected from:

- (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- (3) M wherein M is
 - a) OR^{12} ;
 - b) halogen;
 - c) CF_3 ;
 - d) SR^{12} ;
 - e) $-SOR^{12}$;
 - f) $-SO_2R^{12}$;
 - g) $O-\overset{\overset{O}{\parallel}}{C}-R^{14}$ wherein R^{14} is H, $(CH_2)_nCOOR^{13}$ wherein n is 0 to 4, C_1 to C_6 alkyl, CF_3 , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of R^{12} ; H, C_1 to C_6 alkyl, CF_3 , phenyl

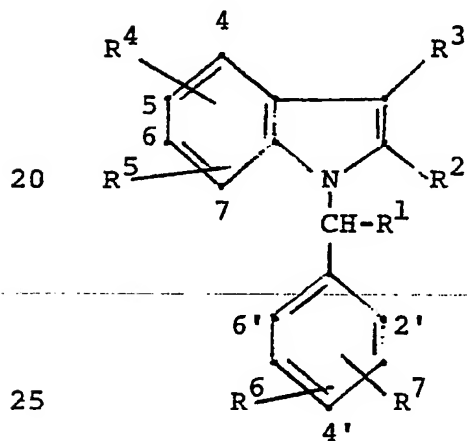
or substituted phenyl wherein
substituted phenyl is as
defined below in the
definition of R^{12} ;

5 h) CN;

each R^{12} is independently H; C_1 to C_6
alkyl; benzyl; phenyl or substituted phenyl wherein
the substituents are C_1 to C_3 alkyl, halogen, CN,
CF₃, COOR¹³, CH₂COOR¹³, wherein R^{13} is H,
10 phenyl; C_1 to C_6 alkyl or C_1 to C_4 perfluoroalkyl;
or a pharmaceutically acceptable salt thereof, and a
pharmaceutically acceptable carrier.

3. A compound of the Formula Ia:

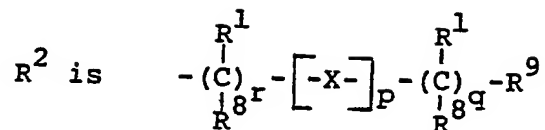
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Ia

wherein:

30 R^1 is H or alkyl of 1 to 6 carbons or R^1 and
 R^8 taken together form a group $(CH_2)_v$
wherein v is 1 to 7;



wherein:

5 each R^8 is independently H, OH, C_1 to C_4 -O-alkyl, or alkyl of 1 to 4 carbons or R^1 and

R^8 taken together form a group $(CH_2)_v$ wherein v is 1 to 7;

10 R^9 is $COOR^1$; CH_2OH ; CHO; tetrazole; $NHSO_2R^{10}$ wherein R^{10} is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbons, halogen, hydroxy, COOH, CN, formyl or acyl to 1 to 6 carbons; $CONHSO_2R^{10}$; hydroxymethylketone; CN; or $CON(R^8)_2$;

15 X is O; S; SO; SO_2 ; NR^{11} wherein R^{11} is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN; CR^1R^8 ;

20 or the unit $\begin{array}{c} R^1 \quad R^8 \\ | \quad | \\ -C \equiv C- \end{array}$ wherein the dotted line represents an optional triple bond and in which the R^1 and R^8 substituents are absent when a triple bond is present;

25 r and q are each independently 0 to 5 and p is 0 or 1 provided that the total of p, q and r is 2 to 6, with the proviso that when R^1 and R^8 are H, X is CH_2 , R^4 is 5-methoxy and R^6 is halogen, then the sums of p, q and r is 3 to 6;

30 R^3 is H, alkyl of 1 to 6 carbons; phenyl or phenyl substituted by R^4 ; or C_1 to C_4 alkyl-

phenyl or C₁ to C₄ alkylphenyl in which the phenyl is substituted by R⁴;

R⁴, R⁵, R⁶ and R⁷ are each

independently selected from:

- 5 (1) hydrogen;
- (2) alkyl having 1 to 6 carbon atoms;
- (3) alkenyl having 2 to 6 carbon atoms;
- (4) $-(CH_2)_nM$
 - 10 a) OR^{12} ;
 - b) halogen;
 - c) CF_3 ;
 - d) SR^{12} ;
 - 15 e) phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of R¹²;
 - f) $COOR^{13}$;
 - 20 g) $\overset{O}{\parallel}C-R^{14}$;
 - h) tetrazole;
 - i) $-\overset{O}{\parallel}NH-C-R^{15}$ wherein R¹⁵ is
 - 25 C₁ to C₆ alkyl, benzyl or phenyl;
 - j) $-NR^{13}R^{13}$;
 - k) $-NHSO_2R^{16}$ wherein R¹⁶ is C₁ to C₆ alkyl,
 - 30 phenyl, or CF_3 ;
 - l) $-\overset{O}{\parallel}C-CH_2OH$;

- 5 m) $-\text{SOR}^{12};$
 n) $-\text{CONR}^{13}\text{R}^{13};$
 o) $-\text{SO}_2\text{NR}^{13}\text{R}^{13};$
 p) $-\text{SO}_2\text{R}^{12};$
 q) $\text{NO}_2;$
 r) $\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^{14};$
 s) $\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}^{13}\text{R}^{13};$
 10 t) $\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}^{15};$
 u) $\text{CN};$

each R^{12} is independently H; C_1 to C_6 alkyl; benzyl; phenyl or substituted phenyl wherein the substituents are C_1 to C_3 alkyl, halogen, CN, CF_3 , COOR^{13} , $\text{CH}_2\text{COOR}^{13}$, C_1 to C_3 alkoxy, or C_1 to C_4 perfluoroalkyl;

each R^{13} is independently H, phenyl or C_1 to C_6 alkyl;

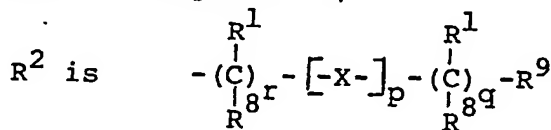
20 each R^{14} is independently H, $(\text{CH}_2)_n\text{COOR}^{13}$ wherein n is 0 to 4, C_1 to C_6 alkyl, CF_3 , phenyl, or substituted phenyl wherein substituted phenyl is as defined above in the definition of R^{12} ; or a pharmaceutically acceptable salt thereof.

25

4. A compound of Claim 3 wherein:

R^1 is H or alkyl of 1 to 3 carbons, with the proviso that R^1 on the benzylic carbon attached to the indole nitrogen is H;

30



wherein:

each R^8 is independently H or alkyl of 1 to 4 carbons, with the proviso that at least one of the R^1 or R^8 substituents in R^2 is not hydrogen;

5 R^9 is COOH; CH_2OH ; CHO; or tetrazole;
 X is CR^1R^8 ;

r and q are each independently 0 to 3 and p is 0 or 1 provided that the total of p , q and r is 2 to 3;

10 R^3 is alkyl of 1 to 6 carbons, but not cycloalkyl;

R^4 , R^5 , R^6 and R^7 are each independently selected from:

- (1) hydrogen;
 15 (2) alkyl having 1 to 6 carbon atoms;
 (3) M wherein M is

- a) OR^{12} ;
 b) halogen;
 c) CF_3 ;

20

- d) SR^{12} ;
 e) $-SOR^{12}$;
 f) $-SO_2R^{12}$;

25

- g) $O-\overset{\overset{O}{\parallel}}{C}-R^{14}$, wherein R^{14} is H, C_1 to C_6 alkyl, CF_3 , phenyl or substituted phenyl wherein substituted phenyl is as defined below in the definition of R^{12} ;

30

- h) CN;

2949P/1039A

- 110 -

17102Y

each R^{12} is independently H; C_1 to C_6 alkyl; or benzyl; or a pharmaceutically acceptable salt thereof.

5 5. A compound of Claim 3 wherein:
 R^1 is H or alkyl of 1 to 3 carbons, with the proviso that R^1 on the benzylic carbon attached to the indole nitrogen is H;

10 R^2 is
$$\begin{array}{c} R^1 \\ | \\ -(C)_{8r} - [-X-]_p - (C)_{8q} - R^9 \\ | \qquad \qquad | \\ R \qquad \qquad R \end{array}$$

wherein:

each R^8 is independently H or alkyl of 1 to 4 carbons;

15 R^9 is $COOH$; CH_2OH ; CHO ; or tetrazole;

X is O; S; SO ; or SO_2 ;

r and q are each independently 0 to 3 and p is 1 provided that the total of p , q and r is 2 to 3;

20 R^3 is alkyl of 1 to 6 carbons, but not cycloalkyl;

R^4 , R^5 , R^6 and R^7 are each independently selected from:

(1) hydrogen;

(2) alkyl having 1 to 6 carbon atoms;

25 (3) M wherein M is

a) OR^{12} ;

b) halogen;

c) CF_3 ;

30

d) SR^{12} ;

e) $-SOR^{12}$;

f) $-SO_2R^{12}$;

- g) $\text{O}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{R}^{14}$, wherein R^{14} is H,
 C_1 to C_6 alkyl, CF_3 ,
 phenyl or substituted phenyl
 5 wherein substituted phenyl is
 as defined below in the
 definition of R^{12} ;
- h) CN;
 each R^{12} is independently H; C_1 to C_6
 10 alkyl; or benzyl;
 or a pharmaceutically acceptable salt thereof.

6. The compounds of Claim 3:

- 3-[1-(p-Chlorobenzyl)-5-chloro-3-methyl-2-indolyl]-
 15 propionic acid;
 3-[1-(p-Chlorobenzyl)-3-methyl-5-fluoro-2-indolyl]-
 propionic acid;
 3-[1-p-Chlorobenzyl-3-methyl-4,6-dichloro-2-
 indolyl]propionic acid;
 20 3-[1-(p-Chlorobenzyl)-3-methyl-4-methoxy-2-
 indolyl]propionic acid;
 3-[1-(p-chlorobenzyl)-3-methyl-6-methoxy-2-
 indolyl]propionic acid;
 25 3-[1-(p-Chlorobenzyl)-3,4-dimethyl-2-indolyl]pro-
 pionic acid and 3-[1-(p-chlorobenzyl)-3,6-
 dimethyl-2-indolyl]propionic acid (as a mixture);
 1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-(4'-carboxy-
 butyl)indole;
 3-[1-(p-Chlorobenzyl)-3,5-dimethyl-2-indolyl]-
 30 propionic acid;
 1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-(3-carboxy-
 propyl)indole;

0166591

2949P/1039A .

- 112 -

17102Y

- 3-[1-(p-Chlorobenzyl)-3-methyl-2-indolyl]propionic
acid;
- 3-[1-(p-Chlorobenzyl)-5-bromo-3-methyl-2-indolyl]-
propionic acid;
- 5 1-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(2-
carboxyethyl)indole;
- 1-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(2-
carboxyethyl)indole S-oxide;
- 10 1-(4-Thiomethylbenzyl)-5-methoxy-3-methyl-2-(3-
carboxypropyl)indole;
- 4-[1-(p-Chlorobenzyl)-3-methyl-5-fluoro-2-indolyl]-
butanoic acid;
- 3-[1-(p-Thiomethylbenzyl)-3-methyl-5-fluoro-2-
indolyl]propanoic acid;
- 15 3-[1-p-Methylsulfoxybenzyl)-3-methyl-5-fluoro-2-
indolyl]-propanoic acid;
- 3-[1-(4-Chlorobenzyl)-3-methyl-5-methoxy-2-indolyl]-
butanoic acid;
- 3-Methyl-4-[1-p-chlorobenzyl-5-methoxy-3-methylindol-
2-yl]butanoic acid;
- 20 3-Methyl-4-[1-p-chlorobenzyl-5-fluoro-3-methylindol-2-
yl]butanoic acid;
- 3-(1-p-Chlorobenzyl-3-methyl-5-methoxyindol-2-yl)-2,2-
dimethylpropanoic acid;
- 25 3-[1-p-Chlorobenzyl-5-hydroxy-3-methylindol-2-yl]-
propionic acid;
- 3-[1-p-Chlorobenzyl-5-acetoxy-3-methylindol-2-yl]-
propionic acid;
- 3-[4,6-dichloro-1-(4-chlorobenzyl)-3-methyl-1H-
indol-2-yl]propanoic acid;
- 30 3-[1-(4-chlorobenzyl)-4-methoxy-3-methyl-1H-indol-
2-yl]propanoic acid;

- 2-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]methoxylacetic acid;
3-[1-(4-bromobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-dimethylpropanoic acid;
5 3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]2-methyl-propanoic acid;
3-[1-(4-iodobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-dimethyl-propanoic acid;
3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-dimethyl-propanol;
10 3-[1-(4-chlorobenzyl)-3-methoxy-5-hydroxyindol-2-yl]-2,2-dimethyl-propanoic acid;
3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-propanol;
15 3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2,2-dimethyl propanoic acid;
3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-3-methyl-propanoic acid;
3-[1-(4-chlorobenzyl)-3-methyl-5-hydroxyindol-2-yl]butanoic acid;
20 Methyl 4-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-butanoate;

3-[1-(4-chlorobenzyl)-3-methyl-4-propyl-5-hydroxyindol-2-yl]-propanoic acid;
25 3-[1-(4-chlorobenzyl)-3-methyl-5-prop-2-enoxyindol-2-yl]-propanoic acid;
3-[1-(4-chlorobenzyl)-3-methyl-5-methoxyindol-2-yl]-2,2-dimethyl-propanoate;
3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2-methyl-butanoic acid;
30 1-(4-chlorobenzyl)-3-methyl-5-methoxy-1H-indole-2-methoxy acetic acid;

- 3-[1-(4-chlorobenzyl)-3-methyl-5-chloroindol-2-yl]-2,2-dimethyl-propanoic acid;
methyl-3[1(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]propanoate;
- 5 3-[1-(4-aminobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid;
4-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl butanoic acid;
- 10 4-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-1H-indol-2-yl]-2,2-dimethyl butanoic acid;
4-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-3-methyl butanoic acid;
- 15 3-[1-(4-chlorobenzyl)-5-hydroxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid;
3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-2,2-dimethyl propanoic acid;
- 20 4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-2,4,3,3-tetramethyl butanoic acid;
4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-4,3,3-trimethyl butanoic acid;
- 25 4-[1-(4-chlorobenzyl-5-fluoro-3-methyl-1H-indol-2-yl)]-2,2,3-trimethyl butanoic acid;
4-[1-(4-chlorobenzyl-5-methoxy-3-methyl-1H-indol-2-yl)]-2,2,3-trimethyl butanoic acid;
- 30 4-[1-(4-chlorobenzyl-5-ethoxy-3-methyl-1H-indol-2-yl)]-2,2,3-trimethyl butanoic acid;
4-[1-(4-chlorobenzyl-5-chloro-3-methyl-1H-indol-2-yl)]-2,2,3-trimethyl butanoic acid;

0166591

2949P/1039A

- 115 -

17102Y

4-[1-(4-chlorobenzyl-3-methyl-5-trifluoromethyl-1H-indol-2-yl)-2,4,3,3-tetramethyl butanoic acid;
4-[1-(4-chlorobenzyl-3-methyl-5-trifluoromethylthio-1H-indol-2-yl)-2,4,3,3-tetramethyl butanoic acid;
3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-2,2,3-trimethyl propanoic acid;
3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-2,3,3-trimethyl propanoic acid;
3-[1-(4-chlorobenzyl)-5-ethoxy-3-methyl-1H-indol-2-yl]-2,2,3,3-tetramethyl propanoic acid;
3-[1-(4-chlorobenzyl)-5-methoxy-3-methyl-1H-indol-2-yl]-2,2,3-trimethyl propanoic acid;
3-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-1H-indol-2-yl]-2,2,3-trimethyl propanoic acid;
3-[1-(4-chlorobenzyl)-5-chloro-3-methyl-1H-indol-2-yl]-2,2,3-trimethyl propanoic acid;
3-(1-p-chlorobenzyl-3-methyl-5-methoxyindol-2-yl)-2,2-diethyl propanoic acid;
3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2,2-diethyl propanoic acid;
3-[1-(4-chlorobenzyl)-3-methyl-5-fluoroindol-2-yl]-2-ethyl propanoic acid;
~~3-[1-(4-chlorobenzyl)-3-ethyl-5-fluoroindol-2-yl]-3-~~
methyl propanoic acid; and
3-[1-(4-chlorobenzyl-3-methyl-5-methoxy-2-indolyl] pentanoic acid.

7. A composition as claimed in Claim 1 for use in the inhibition of leukotriene synthesis in a mammal.
8. A compound as claimed in Claim 3 for use in the inhibition of leukotriene synthesis in a mammal.
9. A composition as claimed in Claim 1 or 2 that additionally comprises a second active ingredient that is a non-steroidal anti-inflammatory drug; a peripheral analgesic agent; a cyclooxygenase inhibitor; a leukotriene antagonist; a leukotriene biosynthesis inhibitor; an H_2 -receptor antagonist; an antihistaminic agent; a prostaglandin antagonist; an ACE inhibitor, or a thromboxane synthetase inhibitor, in which the weight ratio of the compound of Formula I to the second active ingredient is in the range from 1000:1 to 1:1000.
10. A pharmaceutical composition comprising a compound as claimed in any one of Claims 3 to 6 together with a second active ingredient as defined in Claim 9.

(12)

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(71) Applicant: **MERCK FROSST CANADA INC.**
16711 Trans-Canada Highway
Kirkland Quebec(CA)

(72) Inventor: **Guindon, Yvan**
409 Place Closse
Ile Bizard Quebec, H9C 1Y7(CA)

(72) Inventor: **Gillard, John W.**
710 Westchester Drive
Baie d'Urfe Quebec, H9X 2S1(CA)

(72) Inventor: **Yoakim, Christiane**
5770 Cote St. Luc Road, Apt. 12
Montreal Quebec, H3X 2E5(CA)

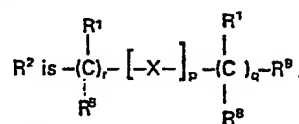
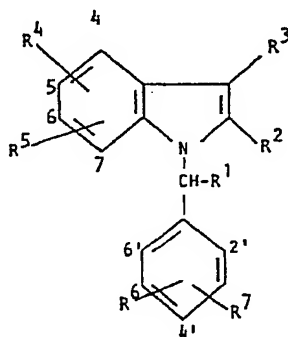
(72) Inventor: **Jones, Thomas R.**
27 Viney Street
Kirkland Quebec, H9J 2T2(CA)

(72) Inventor: **Fortin, Rejean**
4820 Boul. Leger
Montreal Quebec, H1H 1N3(CA)

(74) Representative: **Crampton, Keith John Allen et al,**
D YOUNG & CO 10 Staple Inn
London WC1V 7RD(GB)

(54) Indole-2-alkanoic acids and their use as prostaglandin antagonists.

(57) Compounds of the formula I



where

each R⁸ is independently H, OH, C₁ to C₄-O-alkyl or alkyl of 1 to 4 carbons; or an R¹ and an R⁸ taken together form a group (CH₂)_v, wherein v is 1 to 7,

R⁸ is COOR¹; CH₂OH; CHO; tetrazole; NHSO₂R¹⁰ wherein R¹⁰ is OH, alkyl or alkoxy of 1 to 6 carbons, perhaloalkyl of 1 to 6 carbons, phenyl or phenyl substituted by alkyl or alkoxy groups of 1 to 3 carbons, halogen, hydrocy, COOH, CN, formyl or acyl to 1 to 6 carbons; CONHS₂R¹⁰; hydroxy-methylketone; CN; or CON(R⁸)₂;

X is O; S; SO; SO₂; N¹¹ wherein R¹¹ is H, alkyl of 1 to 6 carbons, acyl of 1 to 6 carbons, CN, CR¹R⁸;



or the unit $-C \equiv C-$ wherein the dotted line represents an optional triple bond and in which the R¹ and R⁸ substituents

where

R¹ is H or alkyl of 1 to 6 carbons or R¹ and R⁸ taken together form a group (CH₂)_v, wherein v is 1 to 7;

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EUROPEAN SEARCH REPORT

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Application Number

EP 85 30 4468

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
Y	CH-A- 455 777 (GEIGY AG) * Whole document *	1	C 07 D 209/22 A 61 K 31/40
Y	CH-A- 454 858 (GEIGY AG) * Whole document *	1	
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 11, no. 6, 25th October 1968, pages 1252-1255, American Chemical Society, US; E. WALTON et al.: "Some analoges of 1-p-chlorobenzyl-5-methylindole-3- -acetic acid" * Page 1253, table I, compound no. 7 *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 209/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 24-03-1986	Examiner MAISONNEUVE J.A.
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